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April 15, 2014

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Corneal Disease Report

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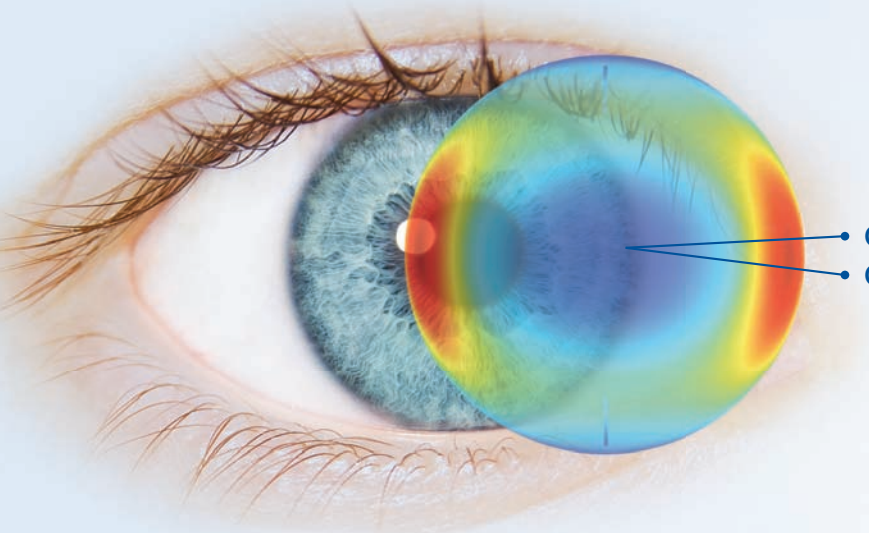

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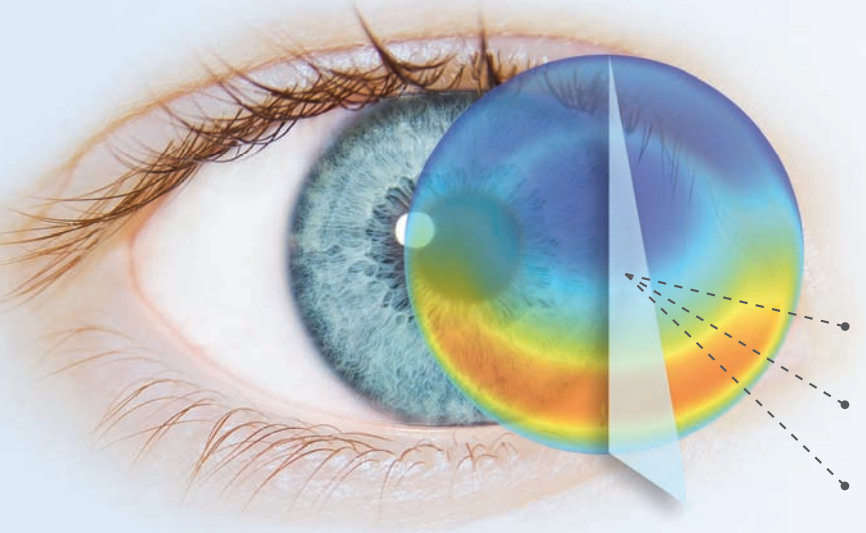

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VOL. 151 NO. 4 ■ APRIL 15, 2014

IN THE NEWS

Congress passed the **Protecting Access to Medicare Act of 2014**, which both pushed back the implementation date for **ICD-10** for another year and also preserved the pay rate for doctors treating **Medicare** patients.

Specifically, the ICD-10 coding revision is now slated for no earlier than October 1, 2015, despite intensive and costly preparations on the part of many hospitals, doctors' offices and health information managers. The new law states that "the Secretary of Health and Human Services may not, prior to October 1, 2015, adopt ICD-10 code sets as the standards for code sets." This means that ICD-10 can start any time after that date.

In addition, the new law also includes yet another temporary fix to the **sustainable growth rate (SGR) formula**, which was approved just hours before a scheduled 24% pay cut to **physicians' Medicare payments** was due to take effect on April 1. Instead, the new law "patched" the SGR with a 0.5% increase in physicians' Medicare payments until December 31, 2014. This is the 17th patch to the flawed SGR formula.

Global rates of **blindness** have fallen sharply over the past two decades, especially in wealthier nations where blindness dropped by half, according to a meta-analysis published online in the *British Journal of Ophthalmology*. Researchers analyzed 243 studies conducted in 190 countries and found that rates of blindness fell by 37% and poor vision by 27% from 1990 to 2010. The most common cause of poor vision remains **uncorrected refractive error**, easily corrected by a pair of eyeglasses.

Can Doxycyline Slow DR Progression?

A daily dose of 50mg of doxycycline appears to inhibit diabetic retinopathy. **By Erin Kelly, Senior Associate Editor**

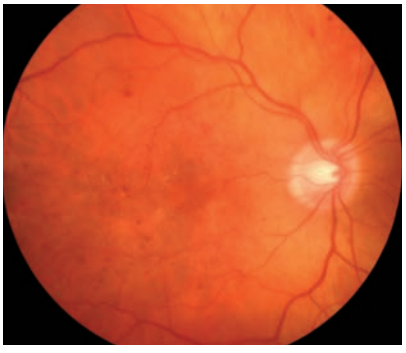
Currently there is no established therapy to slow the progression of non-proliferative diabetic retinopathy (DR), but a small proof-of-concept study by a group of researchers in the US and Denmark shows that low-dose doxycycline can suppress the neuroinflammatory component of DR.

"To our knowledge, this is the first observation suggesting a link between a low-dose oral anti-inflammatory agent and subclinical improvement in inner retinal function," the authors wrote in *JAMA Ophthalmology* online. "Oral doxycycline may be a promising therapeutic strategy targeting the inflammatory component of DR."

Non-proliferative DR is the stage of retinopathy that affects most people with diabetes. Although vascular endothelial growth factor (VEGF) inhibitors may slow progression, they are not widely used and require multiple intraocular injections.

"The significance of the work is the potential ability to treat [DR] with a safe, FDA-approved oral agent and to avoid the necessity for intraocular injections," says lead author Thomas Gardner, MD, professor of ophthalmology and visual sciences at the University of Michigan Medical School, Ann Arbor.

In this randomized, double-masked clinical trial, 30 participants with either type 1 or 2 diabetes mellitus who had at least one eye affected by nonproliferative DR or non-high-risk proliferative DR were given either low-dose (50mg) doxycycline monohydrate or placebo for 24 months.



Doxycycline can suppress the neuroinflammation of diabetic retinopathy.

At the end of the trial, mean foveal sensitivity (as measured by frequency-doubling perimetry) had increased in the doxycycline group (+1.8 dB) and decreased in the placebo group (-1.9 dB). This difference remained significant after adjusting for duration of diabetes. There were no differences between groups regarding other visual function and anatomical outcomes.

Large-scale trials are needed to confirm the findings, the authors say, so doxycycline won't likely be seen in clinical practice just yet.

Scott IU, Jackson GR, Quillen DA, et al. Effect of doxycycline vs placebo on retinal function and diabetic retinopathy progression in patients with severe nonproliferative or non-high-risk proliferative diabetic retinopathy: a randomized clinical trial. JAMA Ophthalmol. 2014 Mar 6. [Epub ahead of print]

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Make Your Smartphone an 'EyePhone'

Think "Instagram for the eye," says assistant professor of ophthalmology Robert Chang, MD, part of a Stanford University School of Medicine research team that recently developed inexpensive adapters enabling smartphones to capture high-quality images of the eye.

The purpose of the adapter is to make it easy for a non-eye doctor to capture a clear picture and immediately share it securely with other practitioners.

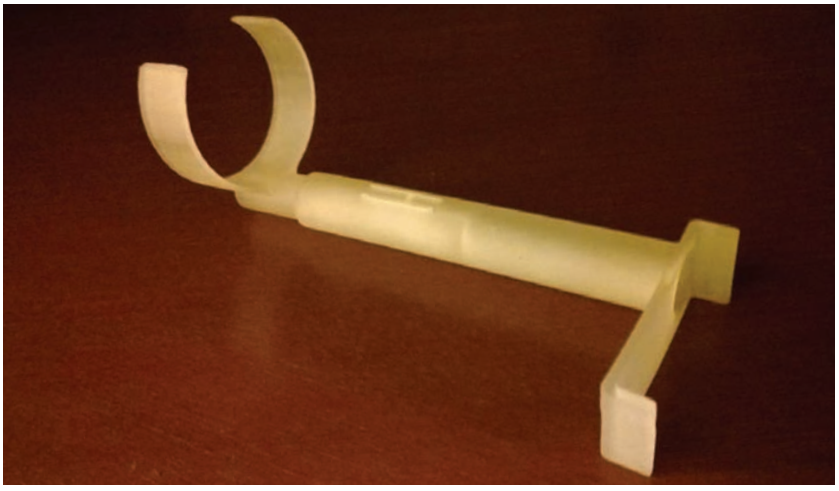
Dr. Chang and his colleagues believe this technology will increase eye care services and improve the efficiency of remote patient consults, particularly in urgent medical situations, as well as in rural, isolated and underserved areas.

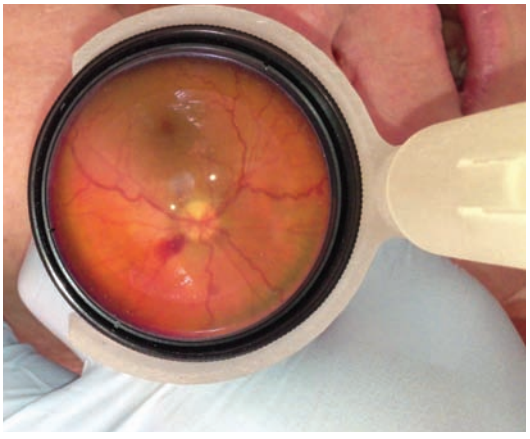
The adapter is inexpensive—about $100—and uses existing ophthalmic lenses for fundus photos.

By comparison, nonmydriatic cameras, either handheld or desktop, cost in the thousands. "When this is not available, then using a high-quality phone image can help with remote triage and save resources and time, if the liability is covered," Dr. Chang says.

Other adapters are available to attach a smartphone to a slit lamp. But Dr. Chang sought to develop technology with point-and-shoot capabilities in seconds, not minutes, with instant upload to secure servers. The researchers also wanted a device that could be used properly by any practitioner, not just eye doctors.

"We basically wanted to remove the need for a slit lamp entirely," Dr. Chang says.





Stanford University doctors created this inexpensive adapter that would even allow non-eye doctors to take images and videos directly from a smartphone.

The adapter is currently designed for the iPhone, but they plan to have versions that work with any modern smartphone with a high-quality camera.

"Others have shown you can hold a lens over the eye and take a video with your smartphone to view the retina—we are basically facilitating that same indirect ophthalmoscopy process but without as much hand-eye coordination needed to obtain the clear picture," Dr. Chang says.

The first prototype was designed to capture images of the anterior segment, but they've now made a posterior segment adapter, too. Both adapters should be available soon, Dr. Chang says.

Myung D, Jais A, Lingmin H, et al. Simple, low-cost smartphone adapter for rapid, high quality ocular anterior segment imaging: a photo diary. Journal MTM. 2014 Feb;3(1):2-8.

For the Record...

Information in an article in our February issue, "A Roundup of Recently Approved Ophthalmic Drugs (and Their Use in Practice)," requires clarification: Simbrinza (brinzolamide 1%, brimonidine tartrate 2%, Alcon) should have been described as a combination of medications from two drug classes that have many inexpensive generic options. Simbrinza does not require refrigeration under long-term storage, but can be stored at 36° to 77°F (2° to 25°C). Also, samples of Simbrinza have not been limited.

Today, she presents with dry eye symptoms.

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For millions of dry eye patients, their symptoms could be an early sign of a progressive autoimmune disease.[1,2]

As many as **1 in 10** patients with dry eye also have Sjögren's Syndrome, a chronic condition of deteriorating exocrine glands that can have significant systemic ramifications.[2-4]

Today, it takes an average of **4.7 years** to receive an accurate diagnosis.[2] Together with the Sjögren's Syndrome Foundation, Nicox is out to change that.

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References: 1. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med*. 2004;164(12): 1275-1284. **2.** Sjögren's Syndrome Foundation. Sjögren's Syndrome Foundation. 2001. Available at http://www.sjogrens.org. Accessed September 5, 2013. **3.** Liew M, Zhang M, Kim E, et al. Prevalence and predictors of Sjögren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol*. 2012;96:1498-1503. **4.** Martin-Martin LS, Massafra U, Migliore A. Sjögren's syndrome: an under-diagnosed disorder. *CLI*. May 2004.

Eye Drops: 'Magic Bullet' for AMD

Researchers may have discovered what they call the "magic bullet" in the treatment of blindness-causing disorders—the successful use of topical eye drops for retinal disease, instead of unpleasant and expensive eye injections.

The findings, conducted in animal models by University College London researchers, indicate that it's possible to create formulations of tiny nanoparticles loaded with Avastin (bevacizumab, Genentech/Roche) to deliver significant concentrations to the posterior segment.

This treatment would be particularly valuable for those who suffer from AMD, which affects an estimated 15 million Americans, according to the National Eye Institute.

More than 1 million intravitreal injections were given in the US in 2010, according to UCL. In the UK, 30,500 injections were estimated to have been given in 2008—a 150-fold increase in 10 years.

Effective delivery of drugs to the retina is considered one of the most challenging areas in ophthalmic drug development, due to anatomical and physiological barriers. "The development of eye drops that can be safely and effectively used in patients would be a magic bullet—a huge breakthrough," says lead researcher Francesca Cordeiro, MD, PhD, of UCL Institute of Ophthalmology.

Researchers are now seeking commercial partners to accelerate development. "All the components we used are safe and well-established in the field, meaning we could potentially move quickly to get the technology into trials in patients. But the timescales are dependent on funding," says the study's lead author Ben Davis, PhD.

The technology has been patented by UCL's technology transfer company, UCL Business.

Davis BM, Normando EM, Guo L, et al. Topical delivery of Avastin to the posterior segment of the eye in vivo using annexin a5-associated liposomes. Small. 2014 Mar 5. [Epub ahead of print]

Legislation in Tennessee to Allow ODs to Use Injectable Anesthetic

New legislation in Tennessee will allow certified optometrists to inject local anesthetic in the eyelid to treat certain lesions.

The Tennessee Medical Association and Tennessee Academy of Ophthalmology vigorously opposed the bills (HB 555 and SB 220), which ultimately passed in both the House and Senate.

In a statement voicing the TAO's opposition, President Mark Melson, MD, said, "performing surgical procedures requiring injectable anesthesia requires the highest level of surgical judgment and the ability to ensure patient safety. The optometry training model is not focused on providing practitioners with the necessary medical education and surgical skill set to provide safe and quality surgical care."

Proponents argued that the legislation provides for greater patient convenience and care. Also, the bill does not expand the therapeutic scope of what ODs in Tennessee can do because they currently use topical anesthetics to perform procedures on the eye and eyelid.

"This legislation faced withering opposition with the legislators and general public of the state of Tennessee being fed copious amounts of untrue and misleading information by both individual and organized ophthalmology—state and national—and the Tennessee Medical Association," says Jeff Foster, OD, chairman of the government relations committee for the Tennessee Association of Optometric Physicians.

The bill now awaits the signature of Tennessee Gov. Bill Haslam.

Laser and Lid Legislation Introduced Again in Louisiana

A House bill (HB 1065) has been introduced in Louisiana that would allow ODs to perform certain laser and lid procedures.

According to James Sandefur, OD, executive director of the Optometry Association of Louisiana, the bill "grants access and consumer choice to the people of Louisiana."

The same bill was defeated last year after the Louisiana State Medical Society and the Louisiana Ophthalmology Association teamed up in opposition, which they are poised to do again.

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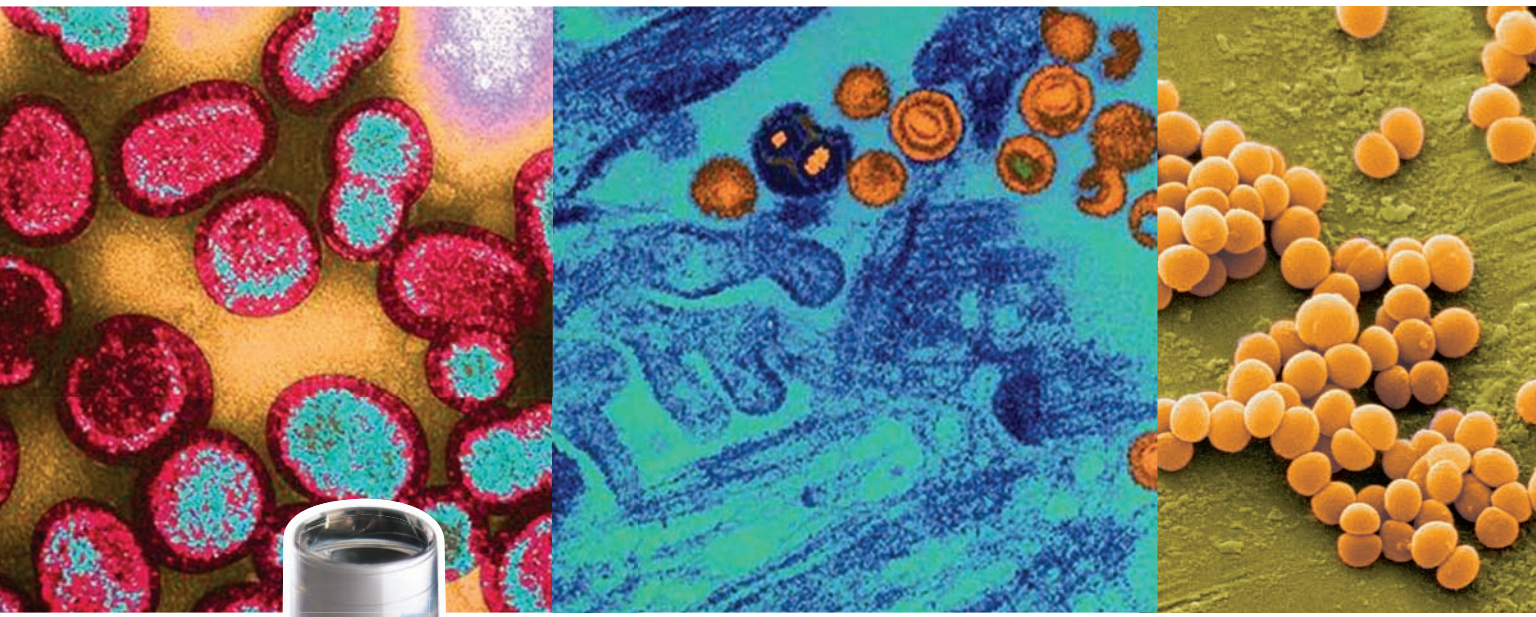

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[1] The Scientific Journal of the Royal College of Ophthalmology

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Color Blindness Most Common in White Boys

White male children have the highest prevalence—one in 20—of color blindness among four major ethnicities, according to a study of more than 4,000 preschoolers, published online in *Ophthalmology*. Color blindness is least common in African-American boys.

Girls of any ethnicity have almost no color blindness—0% to 0.5%—which confirms prior research.

In the study, researchers from the Multi-Ethnic Pediatric Eye Disease Study Group tested 4,005 California preschool children ages 3 to 6. They found the following prevalence for boys of different ethnicities:

- 5.6% of white boys
- 3.1% of Asian boys
- 2.6% of Hispanic boys
- 1.4% of African-American boys

While the researchers found that children at the youngest ages could not accurately complete testing, they say the findings suggest that successful color vision screening can begin at age 4.

Children with color blindness often perform poorly on tests or assignments that use color-coded materials, leading color blind children to be inappropriately classified by ability at school, says the study's principal investigator Rohit Varma, MD, chairman of the Department of Ophthalmology at the University of Southern California Keck School of Medicine.

"It's not that the child is not smart enough or bright enough," Dr. Varma says. "It's that they see the world a little differently."

Children with color blindness can benefit from different kinds of learning materials to demonstrate their understanding of concepts, despite their inability to see colors correctly, Dr. Varma says. "That needs to start early on because labeling a child as not smart or bright enough is a huge stigma for the child and causes significant anxiety for the parents and family," he says.

Xie JZ, Tarczy-Hornoch K, Lin J, et al; Multi-Ethnic Pediatric Eye Disease Study Group. Color vision deficiency in preschool children: The Multi-Ethnic Pediatric Eye Disease Study. Ophthalmology. Article in press. [Epub ahead of print]

Join the Optometric Historical Society

Irving Bennett, OD, extends a personal invitation to all optometrists (especially young ODs) to join the Optometric Historical Society.

Members of the Optometric Historical Society.

"The Optometric Historical Society (OHS) is a very small organization, not quite 50 years old, that exists solely for the purpose of providing original historical research on the profession and practice optometry," Dr. Bennett says. Annual membership dues are $25, which includes a subscription to the organization's quarterly publication, *Hindsight*. Visit the OHS website and download a membership application: www.aoafoundation.org/historical-gems.

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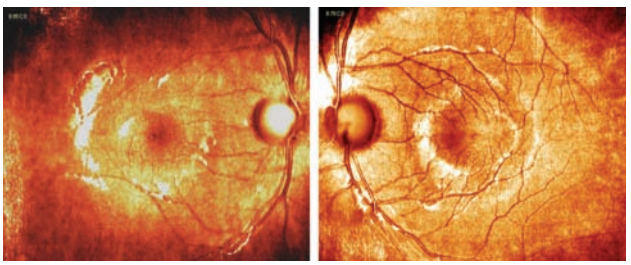

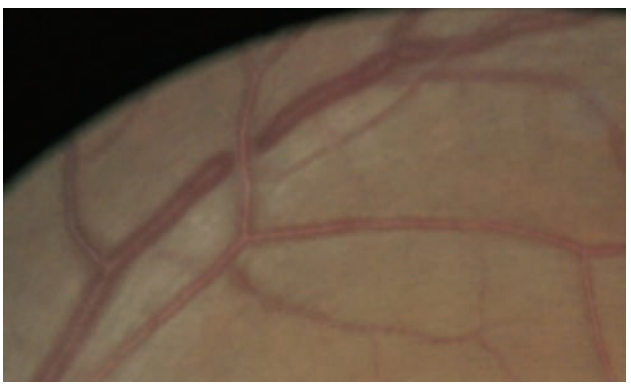

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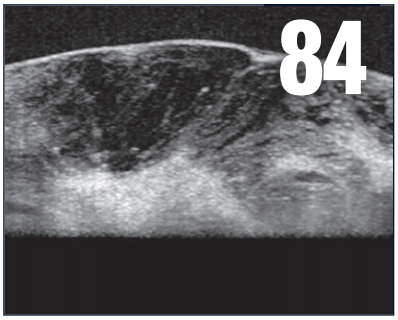

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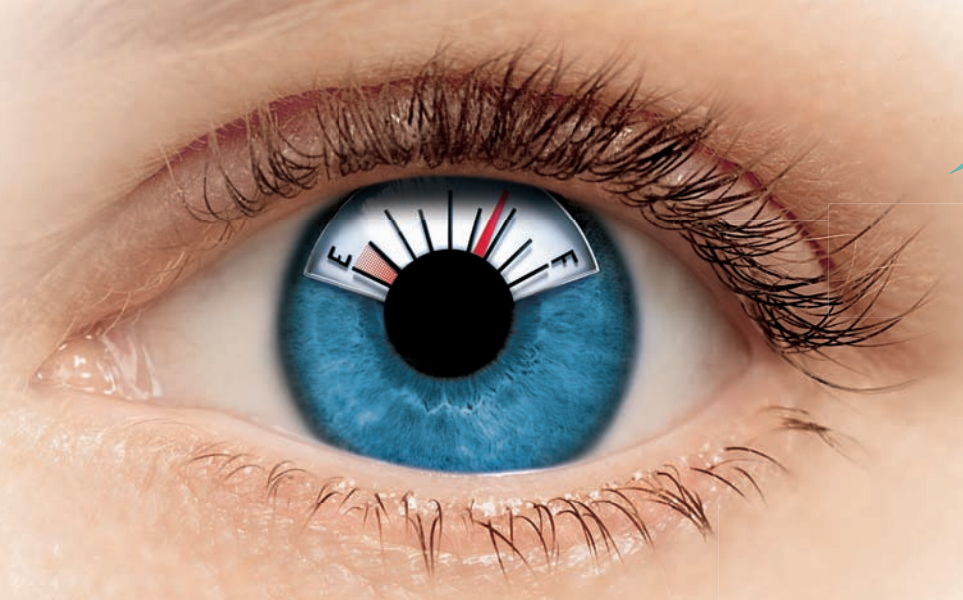

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Use With Contact Lenses: RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion.

Adverse Reactions

In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Please see Brief Summary of the full Prescribing Information on adjacent page.

ALLERGAN

RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%

BRIEF SUMMARY—PLEASE SEE THE RESTASIS® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

RESTASIS® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

CONTRAINDICATIONS

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination

To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces.

Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

ADVERSE REACTIONS

Clinical Trials 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 practice.

In clinical trials, the most common adverse reaction following the use of **RESTASIS®** was ocular burning (17%).

Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Post-marketing Experience

The following adverse reactions have been identified during post approval use of **RESTASIS®**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 5,000 and 32,000 times greater (normalized to body surface area), respectively, than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater (normalized to body surface area), respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 7,000 times greater than the daily human topical dose (0.001 mg/kg/day) normalized to body surface area assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of **RESTASIS®** in pregnant women. **RESTASIS®** should be administered to a pregnant woman only if clearly needed.

Nursing Mothers

Cyclosporine is known to be excreted in human milk following systemic administration, but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of **RESTASIS®** ophthalmic emulsion, caution should be exercised when **RESTASIS®** is administered to a nursing woman.

Pediatric Use

The safety and efficacy of **RESTASIS®** ophthalmic emulsion have not been established in pediatric patients below the age of 16.

Geriatric Use

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis: Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

Impairment of Fertility: No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

PATIENT COUNSELING INFORMATION

Handling the Container

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. To avoid the potential for injury to the eye, advise patients to not touch the vial tip to their eye.

Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

Administration

Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

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Letters to the **Editor**

Generic But Not Equal

The article by Dr. Lighthizer (*"How to Rx the Lowest Cost Drug for Your Patient," February 2014*) was both interesting and informative, but plain misleading. It did not address product performance, manufacturing, professional liability, or concerns about counterfeit products. We feel this article was well intended but does nothing for the patient or the doctor in management. It gives the insurance companies a stronger argument under a false pretense that generic agents are lower in cost and equal in treatment to brand drugs, thus dictating to the physician what he or she can prescribe.

The US Supreme Court has made legal opinions that exempt generic drug manufacturers from liability. A 2011 decision by the US Supreme Court was based on the premise that generic products are identical to brand-name products approved by the FDA. This ruling made generic drug manufacturers not liable for not warning clinicians of safety risks associated with the use of the generic product.[1]

A second opinion came in June 2013 when the US Supreme Court overturned a lower New Hampshire jury that awarded monetary damages to a patient harmed by a generic medication. In this case, the Supreme Court stated that the generic manufacturer had no liability because the FDA had approved the innovator product and the generic medication had provided safety information based on the brand-name product.[2] In the event that the product fails to perform in such a case, who would be liable?

In manufacturing, the chemistry of the innovator or brand product is strictly controlled in the production process, but not so for the generic version. Generic manufacturers are allowed a wider margin of formulation, with acceptable analytical variations typically of 5% of the innovator product, plus variations in inactive ingredients. Often, different manufacturers use their own formulations. This detail makes generics less consistent in therapeutic benefit, safety and effectiveness. The discrepancies can be such that when comparing generic latanoprost to brand-name Xalatan, the average IOP reduction of the generic counterpart was 25% while Xalatan's reduction was 38%, with much fewer adverse events.[3]

Lastly, with the access to foreign pharmacy suppliers, the issue of counterfeit medications is one of concern. In 2012, for example, the FDA warned surgeons of the dangers of counterfeit Avastin.[4]

As clinicians, we are held accountable for both diagnostic and therapeutic outcomes of our patients. Without head-to-head studies, it is difficult to ascertain clinical outcomes of safety and efficacy of generic drugs.

As clinicians, we are held accountable for both diagnostic and therapeutic outcomes of our patients. Without head-to-head studies, it is difficult to ascertain clinical outcomes of safety and efficacy of generic drugs. Unlike systemic medications, it is also difficult to evaluate therapeutic levels of medications in the eye. To the discerning clinician, clinical trials make safety and efficacy data valuable as it guarantees patient safety and clinical outcomes.

With the long history of topical ophthalmic medication failing to perform and new legal implications, it is important that we are both aware and discuss these issues with our patients. Failure to do so is bad medicine.

—Agustin L. Gonzalez, OD, Dallas
Mel Freidman, OD, Memphis, Tenn.

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Dr. Lighthizer responds:

The purpose of the article was to provide doctors an avenue to access potential resources that could allow less expensive medication options for patients, including both generics and cheaper brand names if possible. I was not advocating that all prescribing should be generic, nor should it go the other way and be entirely brand name.

Simply put, many patients have compliance issues and cost is a major factor in that. It was my hope that the article informed doctors of potential resources to research in order to perhaps find a cheaper option for certain patients. ■

19TH ANNUAL

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REVIEW® OF OPTOMETRY

Fit to be Tied

Scope-of-practice battles remind us just how much misrepresentation of optometry still exists. Don't add any of your own. **By Jack Persico, Editor-in-Chief**

While sitting in on a lecture by Jack Schaeffer, OD, and Robert Davis, OD, last month at Vision Expo East, I was pleased to hear Dr. Schaeffer tell a story about how he took a contact lens manufacturer to task for calling optometrists "fitters" in their internal communications about the profession. It's a word that brings to mind shoe salesmen, not doctors entrusted with the health of their patients' eyes.

Dr. Schaeffer felt that sobriquet didn't do him and his colleagues justice, so he took his concerns right to the president—and got results. The company changed its language to be more respectful and accurate in its depiction of optometry.

"Don't be a *fitter*," Dr. Schaeffer implored the Vision Expo audience, "be a *doctor*, be a *professional*." In all your communications—with patients, staff, colleagues—say, "Contact lens *evaluation*, not *fit*."

War of the Words

Words matter quite a bit in determining how others perceive you, and how you perceive yourself. Consider how optometry gets portrayed in scope-of-practice battles.

As this issue went to press, Tennessee was awaiting the governor's signature on a law that will allow optometrists in that state to use injectable anesthetics when managing eyelid lesions. While the legislative outcome was successful, the battle was typically messy, with plenty of potshots lobbed at optometry along the way.

One line in a March 13 news story from *The Daily Herald* of Columbia, Tenn., jumped out at me: "Optometrists examine the eye to prescribe and dispense corrective lenses and perform vision screenings to detect certain eye abnormalities, according to the AAO."

(Cue Frank Sinatra: "It seems to me I've heard that song before. It's from an old, familiar score.")

That disingenuous description of optometry would have been outdated in the 1980s, let alone today. Notice how passive it makes your role sound: optometrists *examine* the eye, perform vision *screenings* and *detect* abnormalities. It continues the decades-long narrative from some in ophthalmology about how an optometrist simply "measures" the eye (after all, it's right there in the profession's name).

Even the use of *abnormalities* feels carefully chosen to marginalize your significance. Yes, optometrists detect "abnormalities"—like AMD, diabetic retinopathy, glaucoma, corneal ulcers, retinal detachments, melanomas and dozens of other threats to ocular and bodily health.

Does that description fairly represent your capabilities, your profession, your role in patients' lives? Not from where I sit. It doesn't describe Aaron Bronner, OD, who wrote for this issue a nuanced and scholarly 5,000-word article on how he and other experts treat corneal infections. Nor does it aptly describe Christopher Suhr, OD, who details what optometrists should know about how hypertension and cholesterol can cause RPE detachment and hypertensive retinopathy, not to mention heart attack and stroke. You know—*abnormalities*.

Nor does it fairly treat the dozens of other optometric educators who share their expertise in *Review*.

And yet, that characterization persists. Talking points disseminated by the Tennessee Medical Association claimed that anesthetic injections performed by ODs could lead to: (1) a perforated globe, "potentially resulting in catastrophic vision loss," (2) injection into a retinal blood vessel, "potentially causing immediate and permanent visual loss," or (3) misdiagnosed cancerous lesions, "potentially resulting in the cancer's spread."

Congrats, Tennessee ODs—the TMA sees much "potential" in you. Too bad it's wholly negative.

In marketing circles, they call this FUD: fear, uncertainty and doubt. It sows seeds of anxiety rather than presenting a balanced discussion.

Organized ophthalmology is, ever so gently, making overtures to optometry of late. That's certainly welcome, but until it comes with a measure of respect, I suggest you hold your applause.

If you don't like what's being said about you, Don Draper once told a client, "change the conversation." Jack Schaeffer did. The Tennessee Association of Optometric Physicians did. You can, too. Control your own narrative. Don't let the FUD persist. And don't devalue your own role either. Because that just doesn't... *fit*. ■

WHAT'S THE SOLUTION?

By Gregory W. DeNaeyer, OD

Topping Off Happens: Disinfection Efficacy Matters

The real-world disinfection efficacy of a multi-purpose contact lens solution can be affected by how it is used – and even by the contact lenses it is used with.

Microbial keratitis is a rare but serious complication of soft contact lens wear. After devastating outbreaks of multi-purpose contact lens solution-related *Fusarium* and *Acanthamoeba keratitis* in 2006 and 2007, the FDA launched in-depth investigations to identify the causes and associated risk factors.

Certain multi-purpose solutions were linked to the outbreaks, but were not themselves contaminated; rather, in some circumstances, they failed to disinfect against pathogens introduced from the environment.[1,2] In addition, patients' failure to follow recommended disinfection practices was found to be a contributing factor in both outbreaks.[2,3]

TOPPING OFF

A critical noncompliant patient behavior identified in these investigations was "topping off," in which, rather than emptying, rinsing, and drying their contact lens cases after each use, patients simply remove the lenses, adding just enough fresh multi-purpose solution to "top off" the case.[2,3]

In a recent survey of 100 soft contact lens wearers, over a quarter of participants reported occasional or frequent topping off.[4] Many subjects were unaware of a solution-related infection risk and thought lens care was only for removing deposits – not microorganisms.[4]

Topping off may contribute to infection risk by multiple interrelated mechanisms. Failing to empty the case and refresh the solution gives contaminating microbes a chance to proliferate.[2] Recent FDA-sponsored studies looked at the impact that uptake and re-use have on multi-purpose disinfection solution efficacy.[1]

KEY POINTS

- Patient noncompliance – especially "topping off" – is associated with reduced multi-purpose solution efficacy.[3]
- In in-vitro testing of a PHMB solution, uptake of disinfectant into the lens reduced the residual concentration of PHMB.[5]
- In similar testing, the residual concentration of POLYQUAD® and ALDOX® was not significantly diminished in the residual solution.[6]

LENS-SOLUTION INTERACTIONS

The ISO/FDA require that a multi-purpose disinfecting solution demonstrate antimicrobial efficacy. Since stand-alone antimicrobial efficacy tests are performed with fresh multi-purpose solution – without exposure to contact lens or a lens case – results may not reflect the impact of lens storage in a lens case.[1] Recent FDA-sponsored research, however, has looked specifically at interactions between contact lenses and multi-purpose solutions, finding that some soft lenses will absorb some preservatives over time, thus diminishing the disinfectant concentration in the solution and reducing its efficacy against some microorganisms.[1,5,6]

DISINFECTION DIFFERENCES

Clavet and coworkers studied the effects of soaking six silicone hydrogel and two hydrogel lens types in a multi-purpose solution contacting the disinfectant polyhexamethylene biguanide (PHMB, 0.0001%, 6-hour soak). Lens cases filled with the multi-purpose solution, but no lenses, served as controls. At intervals of 6, 12, 72, and 168 hours, multi-purpose solution was analyzed for PHMB concentration and biocidal activity against *Fusarium solani*.[1] Certain lens materials (balafilcon A, etafilcon A, and polymacon) absorbed the PHMB, significantly reducing its concentration and lowering the residual solutions' efficacy against *Fusarium*.[1]

A separate, similarly designed experiment also showed depletion of PHMB in the presence of certain lens materials (galyfilcon A, comfilcon A, balafilcon A, polymacon, and etafilcon A), and demonstrated a significant reduction in the disinfecting efficacy against *Staphylococcus aureus*.[5] Reusing and topping off a solution may reduce its antimicrobial efficacy in the presence of a lens.

In similar testing, however, soaking silicone hydrogel and hydrogel lenses in a solution containing the dual biocidal agents polyquaternium-1 (0.001%) and myristamidopropyl dimethylamine (0.0005%) did not significantly reduce residual preservative levels or antimicrobial efficacy against *S. aureus*.[6]

CLINICAL VALUE

Helping patients to be successful in contact lenses requires clear, repeated education about choosing the right lens care solution and suing it properly. I always ask returning patients about their contact lens care; I make sure they are aware of the dangers of topping off, and of differences in multi-purpose solutions.

Recommending a multi-purpose solution and talking about proper lens care and multi-purpose solution use are important first steps. Reinforcing this discussion, as our practice does, with written instructions, gives patients a road map to successful and comfortable contact lens wear. ■

Gregory W. DeNaeyer, OD, practices at Arena Eye Surgeons, in Columbus, Ohio.

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Mo' Employees, Mo' Problems

More employees doesn't equal greater success. For example, take my latest new hire... Please, just take her! **By Montgomery Vickers, OD**

I've written before about how I have had as many as eight employees and two doctors in the office. Interestingly, now that I have a newer, smaller and more efficient office with 2½ employees and little ol' moi, the sole doctor, my satisfaction and also my income is better than at any time when I had a squirming mass of employees crawling all over one another.

The one employee I fired was the sister of one of my best-ever employees, who we trained from scratch.

Before this I had, by and large, decided that my best-ever employees were those who knew nothing about the eye business but who are smart and fun to hang out with. So, sometime after big sis departed for another state, I hired little sis!

Turns out genetics is not a good indicator of talent, which, I guess, is why you never hear anything about Merold Streep, the fishmonger.

To be specific, this employee's whole job was to keep the rooms ready for patient care—make sure the sink was clean, keep the trash from overflowing, reset the phoropters to zero, and so forth. Day after day after day, hardly any of these simple tasks were accomplished. One day, I had a great idea. I made a check-off list. All she had to do was check off what she did when she did it! Every evening, the completed list, signed by her, was placed on my desk. I was thrilled to see it all full of checks.

Except for the fact that she did not actually *do* the tasks that were checked off. She had just checked them off!

I very gently told her to "pack up your crap and get out of my office." I like to think this made my ex-employee a better employee somewhere else.

When I ended up at one point with five employees, my income, gross and net grew. When we dropped to three good people, gross and net incomes grew again!

I decided the secret to success is fire everyone. Imagine what we could make with zero employees!

Less Than Zero

Uh, it turns out that experiment actually did NOT work. Patients hate it when they wander the empty hallways as their sad cries for help echo unheard through the toilet-paperless stalls of your office.

So, we needed somebody who actually worked for us. I tried a few ideas and combinations:

1. I hired two lifelong friends. They have never spoken to one another since.

2. I hired the wife of my rock band's bassist. They immediately moved to another state and broke up. Even worse, we lost a bass player.

3. I broke my own rule and rehired a former employee. Don't. Don't ever. Just don't.

4. I hired one of my best friend's daughters. She left me for college. How lazy is that?

5. I hired a wonderful lady with impeccable credentials who had just moved to our state to avoid a federal warrant for her arrest. Brilliant!

That's when I realized that my best move was to just let my wife, Renee, do all the hiring and her philosophy is just never hire anyone. This has worked perfectly. I have very much enjoyed my unrelationship with my nonemployees these many years, and I wish all of them great success as they undoubtedly create chaos daily in my competitors' offices across the area.

Oh, by the way, we could use one more employee.

Anyone interested? ■

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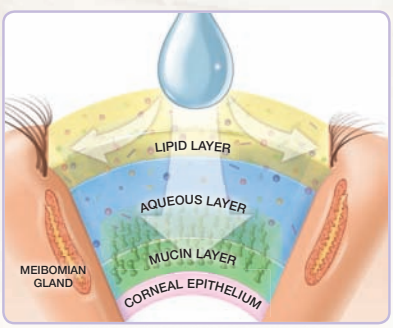

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SYSTANE® Brand products are formulated for the temporary relief of burning and irritation due to dryness of the eye.

References: 1. Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care.* 2013;19 (5 suppl):S67-S75. **2.** Korb DR, Blackie CA, Meadows DL, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy.

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'Tis the Season for Sneezin'

Thanks to the wicked winter, this spring may be a total itch. Prepare your practice to handle a windfall of ocular allergies. **By John Rumpakis, OD, MBA, Clinical Coding Editor**

After the harsh winter we've endured, spring is a welcome sign of better and more pleasant things to come.

Unless you're an allergy sufferer, that is.

In fact, this winter's huge snowstorms and persistent cold weather could mean a delayed spring bloom, which would result in a higher-than-average pollen count this allergy season.[1]

In any year, ocular allergy is an extremely common condition, occurring in up to 40% of the US population.[2] That means two in every five patients who walk into your practice on any given day suffer from symptoms associated with ocular allergy.

So, what's the right approach for us to take in order to provide the best clinical outcomes for our patients, while simultaneously growing our practices?

Take a Seasoned Approach

As with other chronic conditions (e.g., glaucoma), incorporating the appropriate approach to managing ocular allergy is critical for both their success and ours. We must be proactive in managing our patients' care both "in season" and "out of season." But patients are often unaware of the various treatment protocols that we can offer, and many frequently choose to "self-treat" to get relief. We must communicate and maintain our role as their doctors to help them manage these chronic conditions.

Easy as Scratching an Itch

The medical coding and compliance requirements for allergy may be one of the easiest things that we do; so easy, in fact, that we often neglect to bill the patient for our services because we forget to record the basic elements of this valuable clinical care into our medical record.

Keep in mind that you must have a statement (either from the patient or as a doctor-directed visit) that fulfills the chief complaint requirement, which simply means that unless the patient comes in with a frank complaint of ocular itching, edema or hyperemia, the visit cannot generally be classified as a medical encounter.

However, if you discover signs and symptoms of ocular allergy during a routine annual examination, and you initiate or change topical therapy, the subsequent follow-up visit does meet the requirement of a doctor-directed visit for a specific reason—and therefore meets the chief complaint requirements, as well as those of medical necessity.

Coding for ocular allergy usually consists of nothing more than an evaluation and management (E/M) visit code. Most likely, the level of the code is either a 99202/12 or a 99203/13, based upon meeting the criterion for each visit.

Sometimes, a 92012 could be appropriate to use as well, provided that you meet the CPT definition of that code, and that the patient must have a new problem or a complication of an existing condition.

Remember to match the CPT code with an appropriate current ICD-9 diagnostic code and to choose a diagnosis with the highest level of specificity (five digits). For example, a patient presents with symptoms of ocular itching, stringy discharge or even contact lens discomfort or intolerance. After an appropriate history and pertinent physical examination, your diagnosis is chronic allergic conjunctivitis (372.14), and you'd code your office visit with one of the office visit codes mentioned above.

Follow-up evaluations to determine the efficacy of your medical therapy are essential for appropriate long-term management of this chronic condition, and are always billed as a separate office visit.

Ocular allergy is a prevalent part of the primary care that we provide, and it's also economically beneficial for our practices. That's nothing to sneeze at. ■

Send questions and comments to CodingAbstract@gmail.com.

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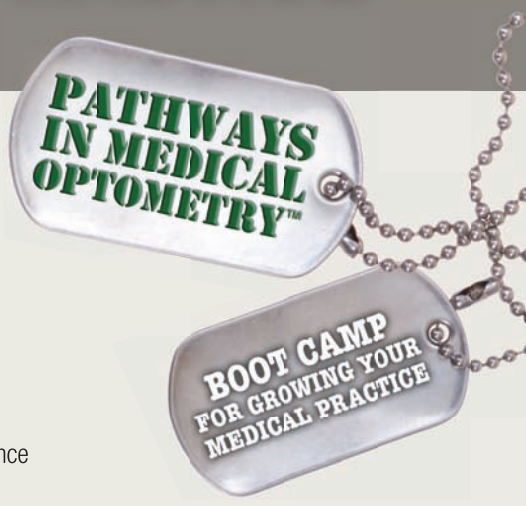

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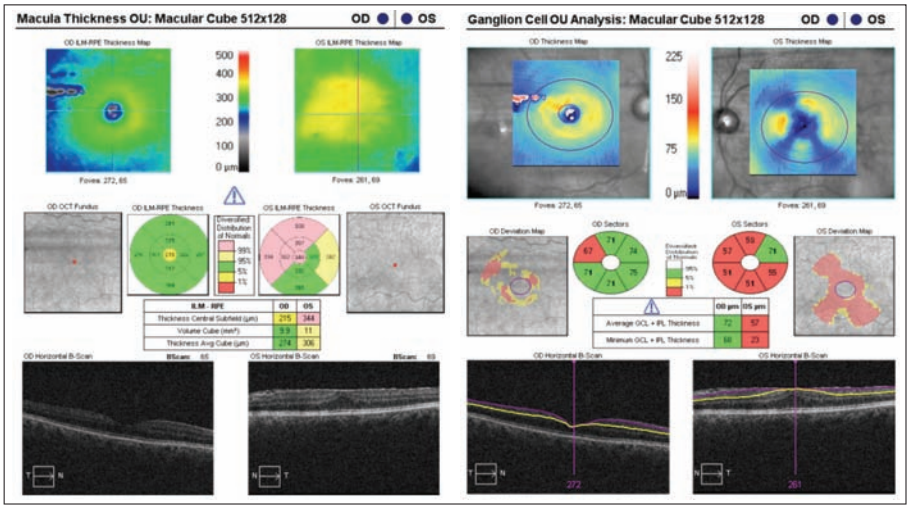
OCT for Glaucoma: Advantages and Artifacts

SD-OCT helps us to identify early structural glaucomatous damage—but watch out for artifacts, particularly due to pathologic features such as an epiretinal membrane.

By Benjamin Casella, OD

Spectral-domain optical coherence tomography (SD-OCT) represents arguably the most significant clinically validated advancement in diagnostic technology that the eye care community has seen for quite some time. The ability to detect, diagnose, stage and determine the rate of progression of eye diseases with a resolution that approaches in vivo histology (much better than magnetic resonance imaging) is a concept about which Helmholtz didn't even dream.



1. Ganglion cell analysis complicated by the presence of an epiretinal membrane.

Over the past several years, SD-OCT has amassed a huge and growing popularity in eye care (and rightfully so). There is no necessary preparation of the tissue being imaged, and very little is required on the part of the patient. The ability to better detect and stage macular edema, along with the ability to examine specific layers of the retina, has proven to be highly beneficial in the care of our patients. Furthermore, SD-OCT arrived on the scene at an opportune time, as the baby boomers are at a point in life at which corneal, lenticular, macular and optic nerve issues are more commonplace.[1]

SD-OCT may be well on its way to becoming standard of care for diseases such as glaucoma. On one hand, detectable structural damage precedes detectable functional damage most of the time.[2] One reason for this may be the presence of overlap in visual receptor fields. Another reason may be that the perfect visual field study just doesn't seem to exist. SD-OCT has already proven to be highly valuable at determining the presence and rate of structural progression.[3] Image registration has proven to be highly beneficial in this capacity.

On the other hand, many patients who need visual field studies (which are still very much standard of care for glaucoma) have cognitive or physical impairments, or both. Combine this with the high level of subjectivity that accompanies a visual field study, and it

For allergic conjunctivitis[1]

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INDICATION AND USAGE

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

IMPORTANT RISK INFORMATION

BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients. BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to any surface. Keep the bottle closed when not in use. BEPREVE® should not be used to treat contact lens–related irritation. Remove contact lenses prior to instillation of BEPREVE®.

The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2%-5% of patients were eye irritation, headache, and nasopharyngitis.

Please see the accompanying prescribing information for BEPREVE® on the following page.

Reference: 1. BEPREVE [package insert]. Tampa, FL: Bausch + Lomb, Inc; 2012.

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For product-related questions and concerns, call **1-800-323-0000** or visit **www.bepreve.com**.

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BEPREVE®
(bepotastine besilate ophthalmic solution) 1.5%

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% safely and effectively. See full prescribing information for BEPREVE®.

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------
Contraindications (4) 06/2012

----------INDICATIONS AND USAGE----------
BEPREVE® is a histamine H1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill one drop into the affected eye(s) twice a day (BID). (2)

----------DOSAGE FORMS AND STRENGTHS--------
Solution containing bepotastine besilate, 1.5%. (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------
- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- BEPREVE should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of BEPREVE. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated. at 1-800-323-0000, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION
Instill one drop of BEPREVE into the affected eye(s) twice a day (BID).

3 DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing bepotastine besilate 1.5%.

4 CONTRAINDICATIONS
Bepreve is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Contamination of Tip and Solution
To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use
Patients should be advised not to wear a contact lens if their eye is red. BEPREVE should not be used to treat contact lens-related irritation.

BEPREVE should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

5.3 Topical Ophthalmic Use Only
BEPREVE is for topical ophthalmic use only.

6 ADVERSE REACTIONS
6.1 Clinical Trials 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 common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

6.2 Post Marketing Experience
Hypersensitivity reactions have been reported rarely during the post-marketing use of BEPREVE. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. The hypersensitivity reactions include itching, body rash, and swelling of lips, tongue and/or throat.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: Teratogenicity studies have been performed in animals. Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day. There were no teratogenic effects seen in rabbits at oral doses up to 500 mg/kg/day given during organogenesis and fetal development (>13,000 times the dose in humans on a mg/kg basis). Evidence of infertility was seen in rats given oral bepotastine besilate 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given 200 mg/kg/day (approximately 3,300 times the topical ocular use in humans). The concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

An increase in stillborns and decreased growth and development were observed in pups born from rats given oral doses of 1,000 mg/kg/day during perinatal and lactation periods. There were no observed effects in rats treated with 100 mg/kg/day.

There are no adequate and well-controlled studies of bepotastine besilate in pregnant women. Because animal reproduction studies are not always predictive of human response, BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

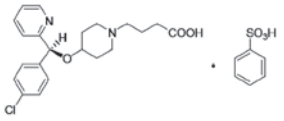
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection limits. The milk concentration was higher than the maternal blood plasma concentration at each time of measurement.

It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is administered to a nursing woman.

8.4 Pediatric Use
Safety and efficacy of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age and from adults.

8.5 Geriatric Use
No overall difference in safety or effectiveness has been observed between elderly and younger patients.

11 DESCRIPTION
BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is a sterile, topically administered drug for ophthalmic use. Each mL of BEPREVE contains 15 mg bepotastine besilate.
Bepotastine besilate is designated chemically as (+) -4-[[(S)-p-chloro-alpha -2-pyridylbenzyl]oxy]-1-piperidine butyric acid monobenzenesulfonate.
The chemical structure for bepotastine besilate is:



Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.
The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mOsm/kg.
Each mL of BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% contains:
Active: Bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
Preservative: benzalkonium chloride 0.005%
Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bepotastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.3 Pharmacokinetics
Absorption: The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% bepotastine besilate ophthalmic solution to both eyes four times daily (QID) for seven days, bepotastine plasma concentrations peaked at approximately one to two hours post-instillation. Maximum plasma concentration for the 1% and 1.5% strengths were 5.1 ± 2.5 ng/mL and 7.3 ± 1.9 ng/mL, respectively. Plasma concentration at 24 hours post-instillation were below the quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups.

Distribution: The extent of protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

Metabolism: *In vitro* metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrate via inhibition of CYP3A4, CYP2C9, and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8, CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9, and CYP2C19.

Excretion: The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels represent systemic exposures approximating 350 and 200 times that achieved with human topical ocular use. The no observable adverse effect levels for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for topical ocular use in humans).

There was no evidence of genotoxicity in the Ames test, in CHO cells (chromosome aberrations), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test.

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and surviving fetuses. Infertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

14 CLINICAL STUDIES
Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (237 patients). BEPREVE (bepotastine besilate ophthalmic solution) 1.5% was more effective than its vehicle for relieving ocular itching induced by an ocular allergen challenge, both at a CAC 15 minutes post-dosing and a CAC 8 hours post dosing of BEPREVE.

The safety of BEPREVE was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING
BEPREVE® (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following size:
5 mL (NDC 24208-629-02)
10 mL (NDC 24208-629-01)

STORAGE
Store at 15º – 25ºC (59º – 77ºF).

17 PATIENT COUNSELING INFORMATION
17.1 Topical Ophthalmic Use Only
For topical ophthalmic administration only.

17.2 Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE should not be used to treat contact lens-related irritation.

Patients should also be advised to remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

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Under license from:
Senju Pharmaceutical Co., Ltd.
Osaka, Japan 541-0046

US/BEP/13/0028 4/13

becomes obvious why the clinician may, at times, be left with less-than-definitive information.

Have I convinced you yet as to why I tuck my SD-OCT in and read it a bedtime story every night when I leave my office?

The Art of Artifact

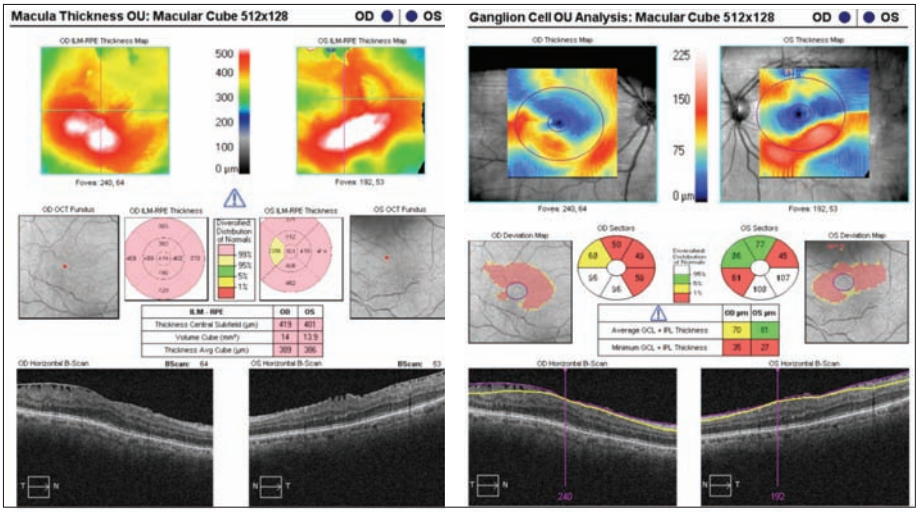
SD-OCT is highly valuable and quite fun, but there are two things it just doesn't do: think and diagnose. Further, it doesn't directly measure the tissues of the human eye. It instead measures differences in the light reflectivity of those tissues.[4] The various tissues, and layers of tissue, in the eye reflect light at different levels, so they show up as distinct entities on an OCT study. However, these different levels of reflectivity do enable the instrument to segment the various components of the tissue being imaged.

For example, the retinal nerve fiber layer (RNFL) is highly optically reflective, while the vitreous humor exhibits a relatively low level of reflectivity (you might call it "optically quiet"). These differences in reflectivity that correspond to the different tissues of the human eye work in favor of the clinician's interpretation most of the time.

However, lurking variables do exist and may lead to misinterpretation if not accounted for.

The presence of artifact is well known to skew interpretations of imaging studies, and SD-OCT is certainly not immune to this concept. In fact, a recent study looking at SD-OCT imaging for glaucoma showed artifacts to be present anywhere from 15% to 36% of the time.[5]

Common artifacts include epiretinal membranes, tractional vitreomacular adhesions, eye movements and media opacities. Normal retinal vasculature may act as artifact, as well.[6]



2. Ganglion cell analysis rendered essentially useless due to epiretinal membranes.

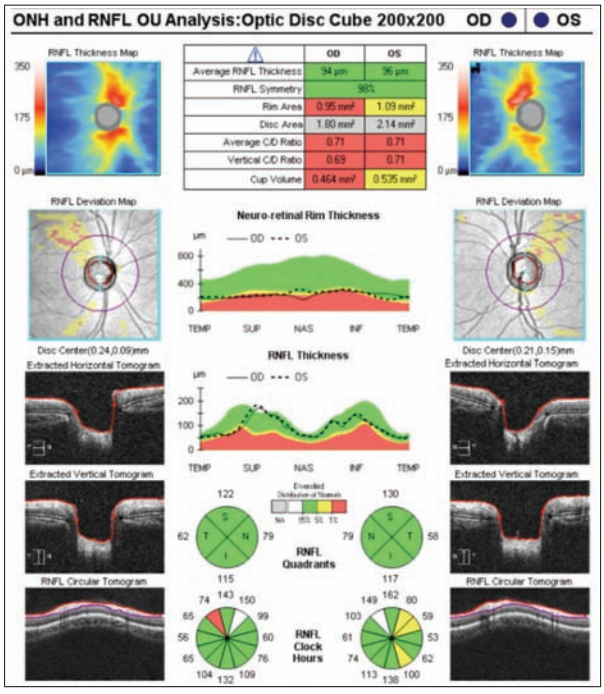
• ***Epiretinal membranes.*** Epiretinal membranes may not always be obvious when viewed with a precorneal lens, and are certainly less obvious via retinal photography. However, they are often seen more easily on SD-OCT studies. An instance comes to mind in which I happened upon an epiretinal membrane by chance while looking at an OCT printout; I had failed to pick it up during funduscopy. It only takes a mild epiretinal membrane to distort the underlying inner retina enough to affect the values of an SD-OCT study, such as ganglion cell analysis.

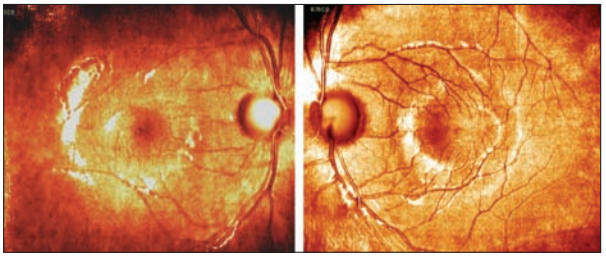
Case in point: A 66-year-old white female presented for a glaucoma work-up and was found to have bilateral epiretinal membranes. The epiretinal membrane on the left macula severely skewed the ganglion cell analysis (*figure 1*). In a similar case of a 65-year-old white male, bilateral epiretinal membranes acted as artifacts, which essentially rendered the ganglion cell analysis useless (*figure 2*).

Epiretinal membranes reflect light in a similar fashion to the innermost layers of the retina (namely the internal limiting membrane). At the very least, they can distort the thickness values of the inner retina. And, although such distortion may only be miniscule, given the high resolution of SD-OCT technology, even a few microns matter. Careful examination of macular studies, in addition to the ganglion cell analysis printout, can aid the astute clinician in avoiding this error.

• ***Uncommon vasculature.*** Anomalous physiologic findings such as epiretinal membranes and vitreomacular adhesions from anomalous posterior vitreous detachments may, at times, have a propensity to skew SD-OCT values with the potential to lull the clinician into a false sense of security or make him or her lean toward a diagnosis that may not be present.

However, congenital findings or "variants on normal" may be misleading, as well. Take this case for instance: An 18-year-old black male was referred to our office as a glaucoma suspect due to enlarged optic





3. Nasalization of retinal vasculature, with corresponding RNFL nasalization, causes points to be flagged in areas suspicious for glaucomatous damage on the RNFL deviation map.

cups. He was mildly myopic with a history that was otherwise noncontributory. Over three visits at three different points in the day, his highest recorded intraocular pressure was 16mm Hg OU. His anterior segments and angles were unremarkable, with no signs of dysgenesis. His SD-OCT studies reflected wedge-shaped areas of his RNFL supero-temporally OU that fell outside of the normative database for his age (*figure 3*). At first glance, these wedge-shaped "defects" appeared to resemble glaucomatous RNFL loss.

However, looking carefully at the vascular patterns in both eyes, it became apparent that the patient had nasalization of his retinal vasculature emanating from his optic nerves with corresponding nasalization of his RNFL. So, this young man's RNFL bundles were very likely healthy; they just weren't where they were "supposed to be," as they followed his vasculature nasally. This particular patient has shown no change in more than two years of follow-up care.

The relative symmetry of this patient's RNFL also points to a variant on normal rather than the presence of pathology. Tilted optic discs often show a similar appearance on OCT studies. Such cases exemplify how normative databases can be both good and not-so-good at the same time. If we take the "stoplight" approach to the OCT printout—green means go (monitor) and red means stop (treat)—then we would end up incorrectly treating this patient as having glaucoma, and not as a false positive (which is the correct diagnosis).

• ***Bergmeister's papilla.*** Another finding that can be overlooked is a subtle Bergmeister's papilla—a small, fibrous tuft that represents a remnant of the hyaloid artery. Bergmeister's papillae, if significant enough, could be mistaken as RNFL, potentially misleading the clinician on interpretation of an SD-OCT optic nerve study.

The TSNIT curve and corresponding tomogram—two areas of the SD-OCT printout that may be overlooked—can indicate the presence of potentially lurking variables, such as subtle Bergmeister's papillae or epiretinal membranes. (*See "SD-OCT Shows NVD—Or is it Something Else?" page 32.*)

SD-OCT technology has truly given us the benefit of quantifying disease processes down to just a few microns (and with little to no effort on the part of the patient). It has augmented how we think about and diagnose several diseases. It will only grow more commonplace as more clinicians make use of it and improvements continue to be made to its already incredible (and

Refer for OCT If Need Be

Because SD-OCT testing is so valuable, many think that this technology should be made available to all patients who may benefit from it. If you haven't yet acquired the technology, but your patient requires SD-OCT, you can still give the patient access to SD-OCT—and you can remain in charge of the patient's care—by means of a referral for testing.

When referring out, the physician who performs the OCT never examines the patient, but only performs the test (and bills one of the OCT codes: 92132, 92133 or 92134, with the -TC modifier for the testing component). The test results return to you, the referring physician, so you can interpret the results and explain them to the patient (and bill for the professional component using the same OCT code along with the -26 modifier).

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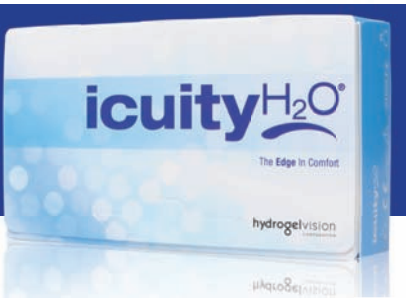


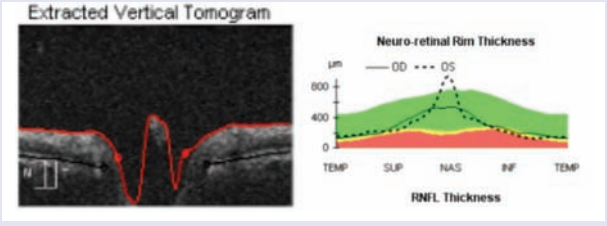
SD-OCT Shows NVD—Or is it Something Else?

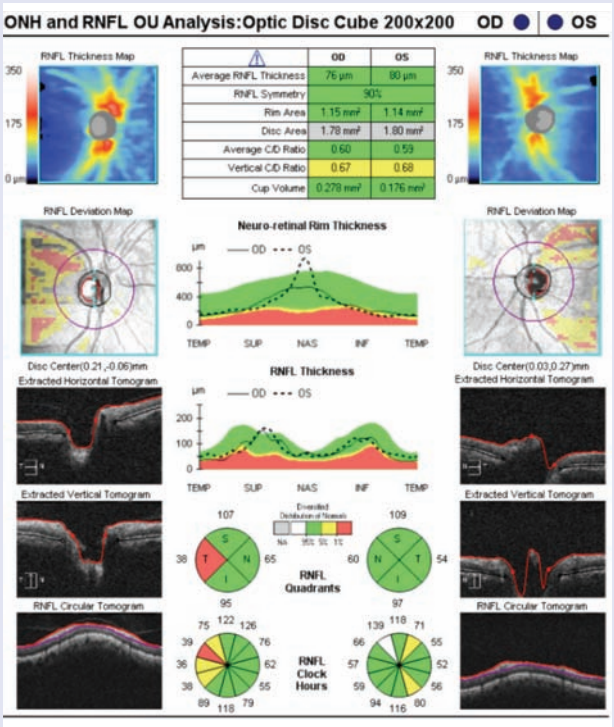
Early in my career, during didactic training—not long after the first SD-OCT was introduced—I had seen a diabetic patient as a request for consultation. I was on my way out of the office when another optometrist stopped me to show me the patient's SD-OCT printout. I wasn't aware, but the patient had been pulled aside for an SD-OCT study after I had both examined him and given him a clean bill of ocular health. The other optometrist informed me that I had missed florid neovascularization of the optic disc.

I'm sure that all color immediately left my face as the patient was being escorted back into an exam room for confirmation of this sinister finding.

Fortunately, after careful evaluation of the patient's optic nerves, it was concluded that I had missed a small Bergmeister's papilla—and not proliferative diabetic retinopathy. I felt bad about missing anything. However, I'm glad that what I had missed turned out to be an incidental finding, and not neovascularization of the optic disc.

On that day, I made a promise to myself that I would try to always look at the patient before looking at the patient's SD-OCT study. Over the years, I've managed to keep that promise (with varying degrees of success).





A Bergmeister's papilla on the left optic nerve, which the OCT incorrectly interprets as RNFL (as evidenced by examination of the extracted tomogram and corresponding TSNIT plot, left).

incredibly fun) functionalities. In addition, advances in the technology may someday allow us to use SD-OCT in place of invasive diagnostic tests, such as fluorescein angiography studies, for certain retinal and optic nerve conditions.[7]

However, SD-OCT technology, as sophisticated as may be, will never yield the same qualitative information as actually looking directly at the tissues of the human eye. For instance, we diagnose people as glaucoma suspects because we've determined that their optic nerves look suspicious for glaucoma. (This is why there is a separate ICD code for "ocular hypertension" that is different from the ones for "glaucoma suspect.")

We then employ the use of tests such as gonioscopy, pachymetry, visual fields and SD-OCT studies to help confirm or deny what we suspect. However, the process for diagnosing disease should, when at all possible, begin with direct evaluation of the tissue in question.

So, SD-OCT technology is an excellent way to achieve objective information (both quantitative and qualitative) in the presence of diseases such as age-related macular degeneration and glaucoma.

However, confounding variables do exist, and it's our responsibility to discern and account for their presence. ■

Dr. Casella is a third-generation optometrist who practices in Augusta, Ga., with an emphasis on ocular disease. He was recently named SECO's Young Optometrist of the South.

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On the Surface: Silicone Hydrogel Lenses and Lipid Deposits

Lipid deposits can degrade contact lens comfort and vision, making it harder to achieve the positive lens wear experience patients expect. But lens materials and surfaces differ, giving some lenses more effective deposit resistance than others. Christopher W. Lievens, OD, MS, FAAO

For many soft contact lens wearers, lipid and protein deposits are important impediments to lasting comfort and lens performance.[1-4] The degree to which any given lens attracts deposits depends on multiple variables, including the lens material.[3] Hydrogel lenses attract mostly protein deposits, while silicone hydrogels adsorb mainly lipids.[2,5]

Lipid deposition can reduce lens wettability, which can aggravate symptoms of contact lens-related dryness and precipitate further lipid deposition.[6,7]

LIPID DEPOSITION

Lipid deposits result from complex interactions between the tear film and the silicone hydrogel polymer. Tear lipids (mainly wax & cholesterol esters, triacylglycerol, with smaller concentrations of cholesterol, fatty acids, and other polar lipids such as phospholipids) comprise approximately 1% to 9% of the tear film and function to maintain its aqueous layer, refractive properties, and resistance to foreign bodies.[8] Silicone hydrogel polymers contain inherently hydrophobic components. In the absence of a surface treatment or material modification, these materials repel water and attract tear lipids.[6]

The adsorption of lipids may begin within hours of lens placement.[7] Free radicals then oxidize the adsorbed lipids, augmenting the hydrophobicity of the lens surface and increasing its coefficient of friction.[6]

Due to rotation about chemical bonds in the silicone hydrogel polymer backbone, lipid deposits on the surface may become absorbed into the inner matrix of the lens.[6] Both on the surface and once embedded in the lens matrix, lipid deposits may be invisible to inspection and go unnoticed by clinicians.

THE AIR OPTIX® CONTACT LENS DIFFERENCE

Developers of silicone hydrogel lenses have employed a range of material modification strategies to mitigate hydrophobicity and lipid deposition. AIR OPTIX® AQUA (lotrafilcon B) and AIR OPTIX® NIGHT & DAY® AQUA (lotrafilcon A) contact lenses, for example, have a unique permanently bonded plasma coating that creates a uniform and uninterrupted hydrophilic surface to resist lipids and maintain wettability.[8] By contrast, surface technology used in balafilcon A lenses results in discontinuous silicate islands and incomplete coverage of the hydrophobic lens matrix.[5] Rather than resisting tear film lipids, a heterogeneous surface may even contribute to lipid immobilization and fouling of the lens.[8]

- Contact lens material, surface treatment, and patient factors all influence lipid deposition
- Lipid deposits may reduce lens wettability, which can interfere with comfort and optics
- AIR OPTIX® contact lenses feature an uninterrupted, permanently bonded plasma surface coating to augment wettability
- Comparison studies show that AIR OPTIX® contact lenses have less lipid deposits than other silicone hydrogels

Studies have repeatedly demonstrated the superior lipid deposit resistance of AIR OPTIX® contact lenses compared with other silicone hydrogels.[1,2,8] In vitro experiments have shown that AIR OPTIX® contact lenses adsorb significantly less cholesterol and phospholipid compared with balafilcon A, galyfilcon A, or senofilcon A lenses.[2,8] In a study of worn lenses, AIR OPTIX® AQUA contact lenses were also associated with significantly less cholesterol deposition than comparator silicone hydrogels, regardless of the lens care solution used.[1]

CLINICAL IMPORTANCE

In practice, some of the complex and dynamic silicone hydrogel lens polymers are susceptible to lipid sorption and spoiling.[6] Lenses with surface treatments that maintain wettability and resist lipid deposits are likely to remain moist and comfortable on the eye.[6] By limiting lipid deposition, such lenses also promote tear film stability, likely reducing contact lens-related dryness.[6,8]

AIR OPTIX® AQUA contact lenses have a uniquely designed surface that enables them to resist lipid deposits about as well as conventional hydrogel lenses.[2] When daily disposable lenses are not an option, selecting a lens with best-in-class lipid resistance may be just the thing to provide the patient with long-term lens wear success.

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How Hypertension and High Cholesterol Harm the Eye

High blood pressure and cholesterol levels can lead to heart attack, stroke and kidney damage. Fortunately, the eye reveals warning signs when trouble's ahead.

By Christopher L. Suhr, OD, MPH

In clinical practice, we encounter a couple of health conditions with such regularity that we may not even think twice when we see the ocular manifestations of them: systemic hypertension and dyslipidemia.

It's well known that hypertension (HTN) and dyslipidemia can lead to many different morbidities, including myocardial infarction, stroke and damage to various systemic organs (most notably the kidneys). Both of these conditions strain the cardiovascular system, which can cause vascular changes that we see frequently in the eye care setting. (Bear in mind that other conditions, namely diabetes mellitus, can have similar retinal changes and should be considered as a differential.)

Fortunately, we can often observe "warning signs" in and around the eyes.

Effects on the Cardio System

To understand the effect of HTN and dyslipidemia in the eyes, we need to understand how these conditions affect the traditional blood flow through the cardiovascular system. Hypertension causes the blood to be forced through the vessels at a greater pressure, while dyslipidemia causes the viscosity of the blood to increase.

• ***Hypertension.*** High blood pressure, or hypertension, is a very common condition that affects an estimated 31.9% of Americans over age 20, according to the Centers for Disease Control and Prevention (CDC).[1]

Blood pressure can be measured with an automated device or a traditional sphygmomanometer and stethoscope. The American Heart Association recommends that blood pressure should be performed on all patients over the age of 20 at every routine exam and every two years regardless of any previous hypertension diagnosis.[2] Two or more measurements of high blood pressure indicate a diagnosis of HTN.[3]

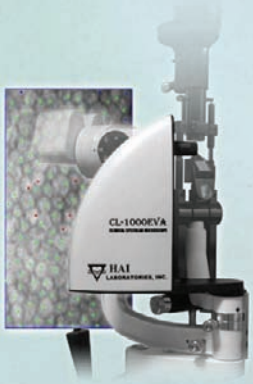
The exception is when malignant hypertension (hypertensive emergency) is present, which is considered a medical emergency and occurs when the systolic reading exceeds 180mm Hg and/or the diastolic number exceeds 110mm Hg.[4] (*See "Classification of Hypertension," page 36.*)

HTN is a major factor in cardiovascular disease because it puts added strain on the heart and vasculature. It also is linked to myocardial infarctions (MI) and cerebrovascular accidents (CVA), or strokes. Further, the stress caused by HTN on the various organs can result in significant damage and even failure. Renal failure is a serious consequence of high

An Introduction to Next-Generation Specular Microscopy

There are approximately 400,000 endothelial cells in the average human cornea.[1] Conventional non-contact specular microscopes available today only sample 40-100 cells in each image, with an effective field of view of less than ~45,000µm squared. That equates to a sample size of only 0.01-0.025% taken within a single area of the central cornea.

As Hirst et al discussed in *Quantitative Analysis of Wide-Field Specular Microscopy: II. Precision of Sampling from the Central Corneal Endothelium*, "The use of specular microscopy as a preoperative evaluative tool in patients is most relevant and commonly practiced in those patients who already have had surgery and have an endothelium with moderate to marked polymegathism. The above sample sizes are unacceptably inaccurate in evaluating the central endothelial density and other parameters."[2]



A New Paradigm: Live Scanning Specular Microscopy

The HAI CL-1000eva is the only non-contact specular microscope available today that shows a live video view of the endothelium. A combination of user-controlled scanning with automated image capture and analysis functions allows the CL-1000eva to overcome many of the problems traditionally found with standalone non-contact specular microscopes, including:

Sample size too small	CL-1000eva can count more than 2x the number of cells, as many as over 300 cells in some samples.
Fixed field of view	Omni-directional scanning provides unlimited FOV before image capture and more than 2x the effective FOV for cell analysis, as much as over 100,000µm^2 in some samples.
Difficulty imaging abnormal cornea	Swelling and other conditions that affect the cornea's thickness and curvature have less of an impact on CL-1000eva's ability to capture usable images.
Difficulty imaging post-transplant surgery	Newer transplant procedures such as Descemet's Stripping Endothelial Keratoplasty can be impossible to image using traditional non-contact specular microscopes, but possible with CL-1000eva.

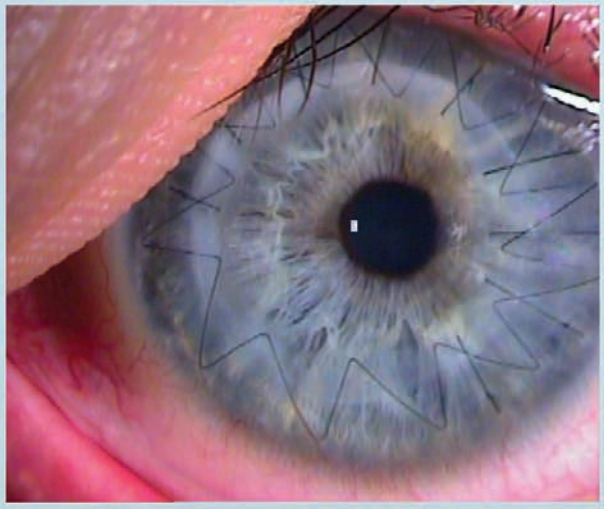


Fig. 1. *Scale representation (white rectangle) of a single specular image captured in the central cornea.*

The Myth of Repeatability

MYTH:	A specular microscope that can repeatedly photograph the same area of the corneal endothelium is believed to be the most accurate.
REALITY:	A single area of the corneal endothelium is not a sufficient sample size to be truly representative of the mean cell density and cell morphology.

Don't Miss Out: Opportunities for Early Diagnosis

In the early stages, progressive corneal diseases such as Fuch's Dystrophy can often go undetected. If a majority of the endothelial cell layer appears healthy and only a small, fixed sample image is taken by the specular microscope, it is possible to miss the warning signs of dystrophy.

Live scanning specular microscopy reveals more of the endothelium in a single exam. This provides greater clinical insights to the doctor.

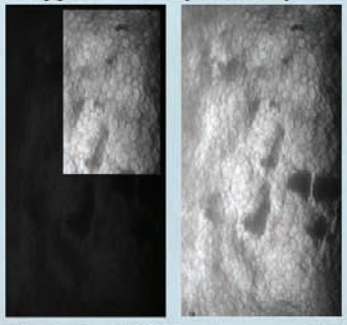


Fig. 2. *Small FOV representation (left) compared to CL-1000eva FOV (right) with 109,909µm^2 countable area.*

About the Manufacturer

Hightech American Industrial Laboratories, Inc. is an ISO certified manufacturer of ophthalmic equipment, and the only company making specular microscopes in the USA. Founded in 1996 and based in Boston, HAI Labs serves governments, universities, hospitals and private practices worldwide by supplying quality products and education.

For more information, visit **www.hailabs.com** or call **(781) 862-9884**.

HAI Laboratories, Inc.

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Classification of Hypertension[4]

BP Classification	Systolic BP		Diastolic BP
Normal	<120mm Hg	and	<80mm Hg
Prehypertensive	120-139mm Hg	or	80-89mm Hg
Stage 1 hypertension	140-159mm Hg	or	90-99mm Hg
Stage 2 hypertension	≥160mm Hg	or	≥100mm Hg
Hypertensive Emergency	>180mm Hg	or	>110mm Hg

blood pressure—especially in the hypertensive emergency phase.

• ***Hyperlipidemia.*** The CDC estimates that 27.9% of Americans have high cholesterol, or hyperlipidemia.[1] With hyperlipidemia, there are typically no symptoms noted by the patient.

Cholesterol is measured by routine fasting blood laboratory analysis. The two most worrisome measures of hyperlipidemia are low-density lipoprotein (LDL) and triglycerides.

Low-density lipoprotein is considered to be the "bad" form of cholesterol (as opposed to "good" high-density lipoprotein) and leads to atherosclerosis, or thickening of the arterial walls. This occurs when the LDL seeps into the arterial walls through damaged junctions of the endothelial cells that line the arterial wall. The residual thickening narrows the channel and decreases blood flow through the vessel, which can lead to an infarction.

Elevated triglyceride levels also can increase the viscosity of the blood. This being the case, triglycerides are often included in the lipid panel for bloodwork and a value of 150mg/dL or less is normal.

Hypertension and the Eye

We know that hypertensive changes can affect the retina, but let's first discuss how it impacts the choroid.

Because the choroidal vasculature does not have the same autoregulation as the retinal vessels, the increase in blood pressure can cause ischemia. This is due to the arterioles in the choroid constricting, resulting in damage to choriocapillaris and the retinal pigment epithelium (RPE), which appear as white areas on the retina (usually in the posterior pole). This causes the release of exudates into the subretinal space, leading to RPE detachment. In these situations, fluorescein shows areas of non-perfusion. In cases of chronic hypertensive damage, Elschnig's spots may appear as RPE hypertrophy with surrounding atrophy.[6]

On the retina, HTN begins with a generalized narrowing of the retinal arterioles due to vasoconstriction. If the blood pressure remains high, the retinal arterioles exhibit an increased light reflex that appears like silver or copper wiring.

Over time, the arteriole and venule interface is changed whereby the arteriole impinges on the venule and causes compression at that point, leading to what is often called arteriovenous (A/V) nicking.

If there is continued hypertensive strain on the vasculature, there can be an eventual loss of autoregulation, resulting in damage to the arteriole endothelial cells and the leakage of plasma and blood contents from the vessels—including exudates. This is the point in which flame-shaped hemorrhages and ischemia are noted on funduscopy. Eventually, optic nerve and retinal nerve fiber layer damage can occur. (This can occur with an acute increase in blood pressure, as in malignant hypertension, or continued chronic HTN.[6])

In the malignant hypertensive state, nerve edema and macular exudates in a stellate pattern may be present.

To help distinguish the level of change in the retina due to HTN, we use the Keith-Wagener-Barker classification system for HTN retinopathy.[6] (*See "Four Stages of Hypertensive Retinopathy," page 38.*) The concern with retinal changes from hypertension is that the strain may result in vessel damage. This is observable in a pending vein occlusion where it can be seen that the arteriole/venous interface causes the flow of the venous blood to be impeded, resulting in a rupture of the vessel and, depending on the location, may result in a branch or central vein occlusion.

The issue with these occlusions is the potential for an ischemic event, yielding the release of vascular endothelial growth factor (VEGF). If left untreated, VEGF may precipitate neovascularization that can cause other vision-threatening conditions, such as macular edema, neovascular glaucoma and fibrosis leading to retinal detachments. When patients present with retinopathy, be sure to refer them to their primary care providers, as they may be at risk for a cardiovascular event.

Hypertensive patients often present with no visual or ocular symptoms. However, some patients do present to eye care providers with vague complaints of headaches, vertigo, lightheadedness, fatigue, intermittent vision changes or blurred vision.

Systemically, there also may be an indication of blood in the urine, dyspnea and chest pain. Even though it is more frequently

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- Corneal vascularization
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- Papillary conjunctivitis

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†The sixth measure was conjunctival staining.

ACUVUE® Brand Contact Lenses are indicated for vision correction. As with any contact lens, eye problems, including corneal ulcers, can develop. Some wearers may experience mild irritation, itching or discomfort. Lenses should not be prescribed if patients have any eye infection, or experience eye discomfort, excessive tearing, vision changes, redness or other eye problems. Consult the package insert for complete information. Complete information is also available from VISTAKON® Division of Johnson & Johnson Vision Care, Inc., by calling 1-800-843-2020 or by visiting acuvueprofessional.com.

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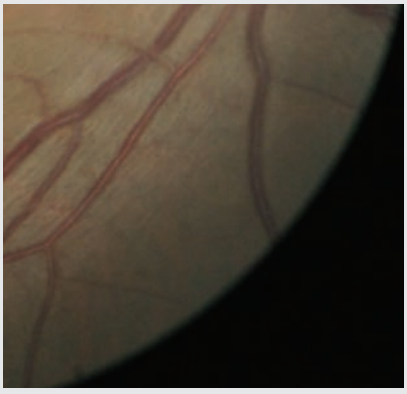
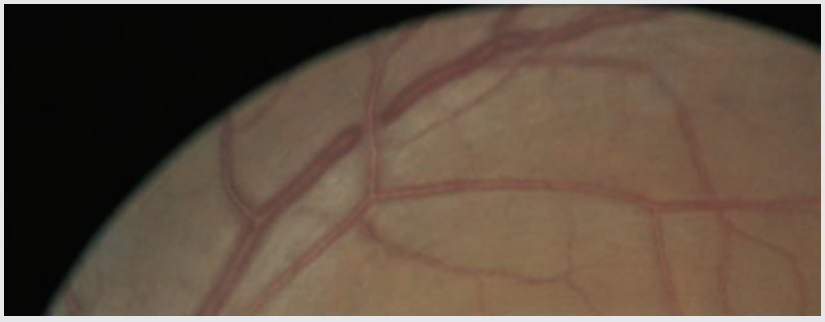
Four Stages of Hypertensive Retinopathy[7]

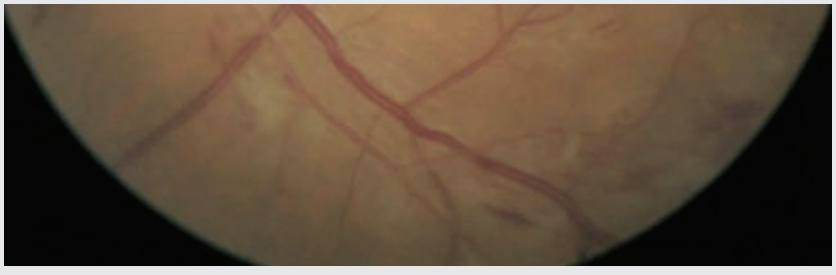
- **Stage 1** is characterized by narrowing of the arterioles, which have the appearance of silver or copper wiring.
- **Stage 2** has the same findings as stage 1, but also includes changes where arterioles cross over venules (referred to as A/V nicking).
- **Stage 3** includes the findings of previous stages, although there are also areas of ischemia (cotton-wool spots) and flame hemorrhages.
- **Stage 4** has the aforementioned findings, but also features optic nerve edema (often with macular star) and is associated with malignant hypertension (also called hypertensive emergency).



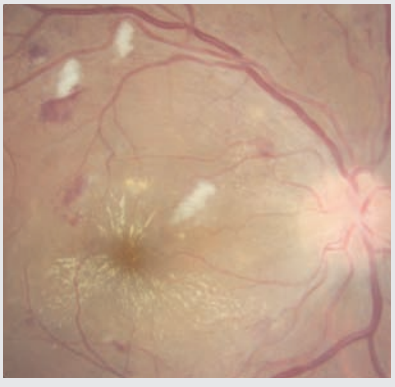
Stage 1 is characterized by narrowing of the arterioles, which have the appearance of silver or copper wiring.



Stage 2 has the same findings as stage 1, but also includes A/V nicking.



Stage 3 also shows ischemia (cotton-wool spots) and flame-shaped hemorrhages.



Stage 4 demonstrates optic nerve edema (with macular star) and is associated with malignant hypertension.

Photos: (Stages 1, 2 and 3) Leo Semes, OD; (Stage 4) Diana Shechtman, OD

reported by those who use anticoagulation medications, some patients present with subconjunctival hemorrhages.[8] As health care providers, we must be vigilant to understand that the ocular signs and visual symptoms may be caused by systemic conditions.

This is important when looking at the morbidity and mortality of HTN. For instance, the three-year survival rate for patients with grade 1 hypertensive retinopathy is 70%, but decreases to just 6% in those with grade 4.[9]

Also, in a 13-year study, the rate of CVA in patients who had any stage of hypertensive retinopathy more than doubled in those with moderate to severe retinopathy. This notable increase in risk correlates directly with higher levels of morbidity, and illustrates the great importance in identifying the various levels of retinopathy to better assess the patient's level of risk.[10]

In addition to the visible changes that clinicians can observe, there are also changes seen on a histologic level. Recent research shows that amyloid beta deposits contribute to the development of macular degeneration. This is important because increased cholesterol has been linked (in animal models) to a greater amount of amyloid beta produced by retinal pigment epithelium cells.[11] In rats that were genetically engineered to have hypercholesterol, researchers found a decrease in retinal ganglion cells along with ischemia, subretinal accumulation of activated macrophages, low grade inflammation and macular edema.[12]

Dyslipidemia and the Eye

Dyslipidemia also causes adverse changes to the eye. Cholesterol emboli may be liberated from plaques within the internal carotid artery and relocate in the retinal arterioles. These emboli, called Hollenhorst plaques, may be associ-

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ated with transient vision loss, or amarousis fugax. These plaques are an important finding because they are linked to a greater likelihood of morbidity and mortality, including transient ischemic attacks.[9,13]

Along with plaques being liberated from the internal carotid, there can also be lipid accumulation in the vessel causing a partial occlusion that can lead to retinal changes that may be seen clinically. This condition is called hypoperfusion retinopathy (or ocular ischemic syndrome) secondary to carotid occlusive disease, and can be accompanied by dot-and-blot hemorrhages in the mid-peripheral retina along with the possibility of neovascularization within the eye.

Treatment

Typically, the treatment for hypertensive retinopathy includes proper management of the underlying condition. So, referral to the patient's primary care provider is warranted when retinopathy is present.

Exercise has long been a means of improving cardiovascular health and lowering blood pressure. Reducing hypertension can also be done with various systemic blood pressure medications, including calcium channel blockers, diuretics, angiotensin receptor blockers, angiotensin converting enzyme (ACE) inhibitors, anti-andrenergics (such as beta blockers and alpha agonists), vasoconstrictors and renin inhibitors.

Pharmaceutical companies have also developed medications that combine classes into a single drug, such as Lotensin HCT (benazepril [ACE inhibitor] and hydrochlorothiazide [diuretic], Novartis).

As with any medication, there are benefits and risks (which are outside the scope of this article)—though be sure to use topical beta blockers with caution when the patient is already taking them systemically (or on another blood pressure medication).

Also use caution in administering 10% phenylephrine in any patient with cardiovascular disease or elevated blood pressure, as phenylephrine has the potential for raising blood pressure.[14] Upon the lowering of the blood pressure back to "normal" levels, there can be regression of the retinopathy in six to 12 months.[9]

If a patient presents with malignant hypertension with concomitant retinopathy, intravitreal bevacizumab (Avastin, Genetech/Roche) along with blood pressure treatment can help to reduce the retinopathy, most notably if there is macular edema.[15]

For dyslipidemia, the course of treatment is also to treat the underlying systemic issue. This is typically done by modifying the patient's diet to reduce cholesterol intake along with exercise and lifestyle changes, such as smoking cessation.[16] If this is unable to fully control the condition, medication is often prescribed, most commonly with statin drugs. There are also other medication classes such as bile acid resins, fibrates, niacin-based drugs and also newer agents that reduce cholesterol absorption in the intestines. Like hypertension meds, some drugs are combination medications of the various classes.

Recently, the American Heart Association and the American College of Cardiology jointly released updated guidelines to help clinicians better manage their overweight and obese patients and those at risk for CVD. Because there is an unquestionable link between obesity and heart disease, the organizations determined that obesity, like CVD, should be treated as a disease and managed by educating the patient to consume fewer calories than the body needs, exercise more and change unhealthy behaviors.

The new guidelines also determined that more patients can benefit from the use of statins. Previously, statins were to be considered if the patient's risk of ischemic event was 20% over 10 years. The guidelines now specify that if that risk factor is lowered to 7.5% over 10 years, and also include women over 60 who smoke and African-American men over 50 with HTN, the levels of cardiovascular disease in America would greatly decrease.[17-19]

With the high prevalence of hypertension and dyslipidemia in the general population, we need to be diligent in the assessment of not only the vague complaints associated with these conditions, but also the signs that may accompany them. Because these systemic conditions have the potential to cause significant damage to not only the

Classification of LDL and Total Cholesterol[5]

LDL Cholesterol (*primary target of therapy*)

<100mg/dL	Optimal
100-129mg/dL	Near optimal/above optimal
130-159mg/dL	Borderline high
160-189mg/dL	High
>190mg/dL	Very high

Total Cholesterol

<200mg/dL	Desirable
200-239mg/dL	Borderline high
>240mg/dL	High

eyes but also to the kidneys, brain and heart, we need to be aware of the importance of proper referrals and monitoring.

After diagnosing ocular changes—and with a concerted effort among the patient's primary care provider, fellow eye care providers and the patient—we can hopefully prevent not only the possible ocular problems from occurring, but also the potential of other organs from being affected beyond repair. ■

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Corneal Disease Report

Don't Let Dangerous Pathogens Resist Arrest

By combining pharmacodynamic principles and advanced drug delivery systems, we can help limit the proliferation of resistant bacteria. **By Richard B. Mangan, OD**

History has shown us that bactericidal resistance is an inevitable consequence of antibiotic use. And as we've seen in recent years, the more frequently you use these drugs, the faster that resistance will develop.

In 2013, officials from the World Economic Forum contended that "the greatest risk to human health comes in the form of antibiotic-resistant bacteria."[1] Representatives from the US Centers for Disease Control and Prevention (CDC) largely agree with this grim assessment and suggest that inappropriate antibiotic use by both patients and physicians is a major contributing factor to escalating rates of microbial resistance.[2]

So, how can we best address this problem and limit the proliferation of resistant bacteria? For starters, clinicians must be more judicious when prescribing antibiotics for their patients. Additionally, we need to consider drug delivery models that best address any possible barriers to compliance—especially in patients who are most likely to be carriers of resistant bacteria.

The Roots of Resistance

One frequently cited explanation for increased rates of bactericidal resistance is unwarranted antibiotic prescribing for the management of cold- or flu-like symptoms. For example, CDC researchers have suggested that approximately 85% of all upper-respiratory infections are viral in nature, and that the use of antibiotics in these instances is superfluous and ineffective.[2]

According to a global survey of prescribing doctors published in 2007, the three main reasons for overprescribing antibiotics for viral infections included diagnostic uncertainty, time/pressure-related demands and patient request.[3] Furthermore, the survey indicated that even when antibiotics are appropriately prescribed, patients aren't always compliant with the recommended treatment regimen. Specifically, the data showed that roughly one out of five patients stopped taking their antibiotics earlier than prescribed because "they started feeling better."[3]

The prophylactic use of topical antibiotics following ocular surgery or at injection sites also may precipitate resistance. In 2011, Stephen Kim, MD, and associates determined that repeated exposure to topical fluoroquinolones and azithromycin after intravitreal anti-VEGF injection was associated with increased multi-drug resistance in coagulase-negative *Staphylococci* (CNS).[4] Additionally, his research team noted that

more than 80% of CNS isolates were resistant to at least three antibiotics, and that more than 65% were resistant to at least five antibiotics.[4]

Basic Pharmacodynamics

To better understand how antibiotic agents eradicate bacteria and fight infection, it is important to distinguish between pharmacokinetics (PK) and pharmacodynamics (PD). Pharmacokinetic measurements are used to calculate the half-life of antimicrobial concentrations in the body, while pharmacodynamic measurements help researchers evaluate the relationship between those concentrations and their comprehensive antimicrobial effect.

Traditionally, antibiotic dosing regimens have been determined by PK parameters only—such as rates of drug absorption, distribution, metabolism and elimination. However, PD measurements have become increasingly important within the last decade because they may be strategically employed to counteract or prevent resistance.

Three key PD metrics frequently used to enhance the therapeutic efficacy and bactericidal activity of antibiotic agents are:[5]

- ***T> MIC***, or time above the minimum inhibitory concentration (MIC), is used to measure the duration a drug remains available at a concentration that's greater than the MIC for a given pathogen. This parameter also is used to define the time-dependent killing of a pathogen.
- ***AUC:MIC ratio*** is the relationship between the area under the curve (i.e., the total exposure of an antibiotic to an organism) at 24 hours and the MIC.
- ***Cmax:MIC*** is the maximum detectable concentration of the drug in target tissue following dosing, with respect to the MIC.

The relative importance of each PD parameter to a drug's antibacterial activity varies among agents.[5] For the fluoroquinolones, researchers have estimated that a Cmax:MIC_{90} ratio of at least 10 and an AUC:MIC_{90} ratio of at least 100 are required to predict microbiological and clinical efficacy (*see "Moxi's MICs for MRSA," page 44*).[6]

The Skinny on MICs

Antimicrobial minimum inhibitory concentrations (MICs) are measures used by scientists to compare the antibiotic efficacy of various agents. MIC values established by the Clinical and Laboratory Standards Institute provide breakpoints where micro-organisms are considered susceptible, intermediately resistant or resistant. For topical agents, the MIC_{90} value—or the score required to inhibit bacterial growth in at least 90% of targeted strains—is considered the gold standard measurement of antibiotic efficacy.

When managing ocular infections, it is essential that we remember that conventional MIC data is based on concentration levels that would be achieved through systemic administration of an antibiotic. Because the eye offers a number of unique barriers to drug absorption, MIC data obtained through in vitro lab analysis does not accurately illustrate the agent's complete pharmacodynamic impact on ocular infections.

Limitations of Empirical Treatment

In an ideal world, eye care professionals would have access to point-of-care diagnostic systems that would identify the causative organism within minutes of culturing. Then, such a system could offer guidance with regard to which antibiotic(s) would be the most appropriate. Until that day arrives, however, clinicians will be forced to rely on standard culture and sensitivity testing via local laboratories and hospitals.

Considering growth and replication rates for most bacterial species, standard culture and sensitivity testing usually takes three or four days to provide information. Given this delay, we're often forced to treat suspected bacterial infections empirically.

While assumptions can be made about what pathogen(s) are involved based on the nature and location of the infection, a diagnosis made on clinical appearance alone is not always reliable. Further, without having the culture results in hand, the organism's possible level of bactericidal resistance is largely indeterminable.

Therefore, whether faced with a sight-threatening infection or the need for prophylaxis around surgery, doctors most often turn to the latest generation topical fluoroquinolones—moxifloxacin, gatifloxacin and besifloxacin. These agents are a fairly safe bet, because they are very well tolerated (even at frequent dosing intervals) and offer an enhanced spectrum of activity against the most common ocular pathogens.

Nonetheless, without positive culture results, even frequent use of the most advanced fluoroquinolones can increase the likelihood of microbial resistance.

Challenges of Ocular Drug Delivery

The average tear film is approximately 7µL by volume. When a single eye drop (30µL to 50µL) is applied to the eye, a fair amount of drug is lost through epiphora and rapid tear clearance secondary

Moxi's MICs for MRSA

Moxifloxacin is commercially available in a 0.5% solution (Moxeza, Alcon Labs). This percentage concentration equates to 5mg/ml, or 5,000µg/ml.

According to the Ocular TRUST study, moxifloxacin's MIC_{90} value for methicillin-resistant *Staphylococcus aureus* (MRSA) is 8µg/ml.[14] However, data from other MIC-tracking research groups suggest that the MIC breakpoint of 8ug/ml might be too low to kill certain ocular pathogens.[15,16]

In 2009, Antibiotic Resistance Management of Ocular Organisms (ARMOR) study researchers evaluated 200 *S. aureus* organisms and determined that 31% were not only resistant to methicillin, but also fluoroquinolones.[15] In ARMOR, the fluoroquinolone MIC_{90} values for ocular MRSA were established at 256µg/ml for ciprofloxacin, 32ug/ml for moxifloxacin and 4µg/ml for besifloxacin.[15]

Another study group examined several MRSA subtypes, and found that strains with the staphylococcal cassette chromosome type II were multidrug resistant against the following MIC_{90} values: 256µg/ml for ciprofloxacin, 128µg/ml for gatifloxacin, 64µg/ml for moxifloxacin and 4µg/ml for besifloxacin.[16]

Nonetheless, it appears that the drop concentration of moxifloxacin (5,000µg/ml) still far exceeds the MIC_{90} for ocular MRSA infections.

As an aside—if we then take a look at projected Cmax/MIC ratios for moxifloxacin in relation to MRSA over time, our ideal target goal of a Cmax/MIC of >10 becomes far less realistic when dealing with MIC_{90} values of 32µg/ml or higher.[6]

Cmax/MIC Ratio for Topical Moxifloxacin (ideal >10)

	MIC_{90} = 4µg/ml	32µg/ml	64µg/ml	128µg/ml
Time				
30 seconds	163	20	10	5.1
1 minute	75	9.4	4.7	2.3
3 minutes	37.5	4.7	2.3	1.2

to reflex blinking. These actions, in turn, contribute to decreased drug bioavailability.[7]

In addition, systemic absorption further promotes topical drug loss. Such inadvertent uptake may occur either directly through blood capillaries in the conjunctiva or indirectly via the nasolacrimal duct system.[8]

Because of the eye's rapid tear clearance mechanism, patients who use topical agents with high drug concentrations and poor retention times intermittently experience low or even undetectable medication levels on the ocular surface. So, if the patient or caregiver fails to administer the drops according to the indicated dosing schedule, drug concentrations may fall below the levels necessary to kill the pathogen and avoid relapse.

Novel Delivery Systems

Former US Surgeon General C. Everett Koop is credited with a highly profound assertion: "Drugs don't work in patients who don't take them."[9] With specific regard to topical ophthalmic drugs, this statement couldn't be more accurate. In my experience, it is much easier to ensure that patients swallow pills than instill drops in their eyes. Fortunately, advanced topical drug delivery systems may help our patients clear this hurdle. Here are a few of note:

• ***DuraSite***. In an effort to combat poor compliance and low drug retention times, topical medications may be combined with a sustained drug delivery vehicle, such as DuraSite (InSite Vision). To date, two commercially available anti-infective agents have been formulated with the DuraSite vehicle—AzaSite (azithromycin, Merck) and Besivance (besifloxacin, Bausch + Lomb).

The mucoadhesive properties of the DuraSite vehicle facilitate enhanced drug residence times on the ocular surface. This, in turn, yields increased drug concentrations on the eye and improved clinical efficacy between dosing applications.[10,11]

• ***Sustained-release plugs***. Ocular Therapeutix, Inc., currently is pioneering a novel punctal plug drug delivery system. The plug slowly delivers therapeutic levels of a drug to the ocular surface over a period of seven to 10 days as it dissolves. These plugs could be ideal for patients with tremendously poor compliance, such as those with severe arthritis or cognitive impairment.

In Phase I testing, researchers developed a single-arm, one-dose study in which 10 patients received a moxifloxacin-saturated punctal plug immediately following cataract surgery.[12] Subjects were monitored over a 10-day period.

Primary outcome measures were plug retention and moxifloxacin levels above MIC levels required to halt the growth of various bacterial strains associated with conjunctivitis.

At the study's conclusion,

If only you could predict how ocular inflammation will behave.

DUREZOL® Emulsion has head-to-head data vs prednisolone acetate in patients with endogenous anterior uveitis.[1]

Scan the QR code with your smartphone or log on to **www.inflammationhappens.com** to see the results for yourself.

INDICATIONS AND USAGE: DUREZOL® Emulsion is a topical corticosteroid that is indicated for:

- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

Dosage and Administration

- For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
- For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

IMPORTANT SAFETY INFORMATION

Contraindications: DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions

- Intraocular pressure (IOP) increase – Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Cataracts – Use of corticosteroids may result in posterior subcapsular cataract formation.
- Delayed healing – The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Bacterial infections – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Viral infections – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Contact lens wear – DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Most Common Adverse Reactions

- Post Operative Ocular Inflammation and Pain – Ocular adverse reactions occurring in 5-15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.
- In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion, please refer to the brief summary of prescribing information on adjacent page.

DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

The results you want. The relief they need.

Alcon®
a Novartis company

Reference: 1. DUREZOL® Emulsion package insert.

DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Ocular Surgery
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.
Endogenous Anterior Uveitis
DUREZOL® Emulsion is also indicated for the treatment of endogenous anterior uveitis.

DOSAGE AND ADMINISTRATION
Ocular Surgery
Instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

Endogenous Anterior Uveitis
Instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

DOSAGE FORMS AND STRENGTHS
DUREZOL® Emulsion contains 0.05% difluprednate as a sterile preserved emulsion for topical ophthalmic administration.

CONTRAINDICATIONS
The use of DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

WARNINGS AND PRECAUTIONS
IOP Increase
Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts
Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections
Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral Infections
Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections
Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Topical Ophthalmic Use Only
DUREZOL® Emulsion is not indicated for intraocular administration.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

ADVERSE REACTIONS
Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects; posterior subcapsular cataract formation; secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular Surgery
Ocular adverse reactions occurring in 5-15% of subjects in clinical studies with DUREZOL® Emulsion included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1-5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in < 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

Endogenous Anterior Uveitis
A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL® Emulsion. The most common adverse reactions of those exposed to DUREZOL® Emulsion occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2-5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects
Pregnancy Category C. Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal) anomalies when administered subcutaneously to rabbits during organogenesis at a dose of 1–10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL® Emulsion, since DUREZOL® Emulsion is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL® Emulsion should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

Nursing Mothers
It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when DUREZOL® Emulsion is administered to a nursing woman.

Pediatric Use
DUREZOL® Emulsion was evaluated in a 3-month, multicenter, double-masked, trial in 79 pediatric patients (39 DUREZOL® Emulsion; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL® Emulsion to prednisolone acetate ophthalmic suspension, 1%.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, and Impairment of Fertility
Difluprednate was not genotoxic *in vitro* in the Ames test, and in cultured mammalian cells CHL/IU (a fibroblastic cell line derived from the lungs of newborn female Chinese hamsters). An *in vivo* micronucleus test of difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 mcg/kg/day prior to and during mating did not impair fertility in either gender. Long term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

Animal Toxicology and/or Pharmacology
In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicity tests of difluprednate showed systemic effects such as suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin; all of which were due to the pharmacologic action of the molecule and are well known glucocorticosteroid effects. Most, if not all of these effects were reversible after drug withdrawal. The NOEL for the subchronic and chronic toxicity tests were consistent between species and ranged from 1–1.25 mcg/kg/day.

PATIENT COUNSELING INFORMATION
Risk of Contamination
This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the emulsion. Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Risk of Secondary Infection
If pain develops, or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Patients should be advised to remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

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U.S. Patent 6,114,319

Manufactured For:
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pharmacokinetic data indicated that tear sample drug levels were maintained between 2,000ng/ml and 3,000ng/ml over a seven-day duration in all 10 patients. These concentration levels are well above the MIC_{90} necessary to inhibit the bacterial growth of *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pneumoniae*.[12]

• ***Contact lens delivery systems.*** Whether employing nanotechnology or differing biodegradable polymers such as PLGA acid, drug-eluting contact lenses can deliver therapeutic levels of antibiotic agents for up to one month.

Daniel S. Kohane, MD, and associates evaluated release medium from dual-polymer lenses that contained ciprofloxacin.[13] The samples were collected after 28 days of use, and were tested against *S. aureus* isolates.

Ciprofloxacin showed complete killing of the *S. aureus* at an inoculum of 10^5 cells.[13] It is important to note that, even at higher inoculum levels, the antibiotic still yielded complete bacterial inhibition—but rare isolates grew at low counts because of emerging bactericidal resistance.

The authors suggested that the drug release rate could be specifically customized by adjusting the molecular mass of the contact lens polymer as well as the volume of medication within the lens coating.[13]

Due to the limitations of standard culture and sensitivity testing, most ocular infections are treated empirically with broad-spectrum antibiotics.

However, the "shotgun" method of bacterial eradication—coupled with the rapid tear clearance of topical drops—can facilitate increased bactericidal resistance. Fortunately, novel drug delivery platforms that effectively incorporate pharmacodynamic research may successfully slow this trend. ■

Dr. Mangan is a fellow of the American Academy of Optometry and is board-certified in medical optometry. He's also the founder of Beaumont Eye Consultants, LLC in Lexington, Ky. He has no direct financial interest in any of the products mentioned.

Vigamox Victorious Over Quinolone-Resistant *S. Aureus*

A 65-five-year old white male presented with a chief complaint of pain, along with light sensitivity and redness OD five days after receiving his eighth Avastin (bevacizumab, Genentech/Roche) injection for macular degeneration.

His best-corrected visual acuity measured 20/80 OD and 20/25 OS. Slit-lamp biomicroscopy revealed a small corneal infiltrate OD, with a shallow, overlying epithelial defect located 5mm inferotemporal to the visual axis. Additionally, we noted mild, underlying edema with trace folds.

He exhibited 1 to 2+ bulbar conjunctival injection OD, with no cell and flare. When asked if he was using his Vigamox (moxifloxacin, Alcon) drops as prescribed (QID for five days OD), the patient confessed that he had exhausted his medication supply the night of his last injection and was slow to have the prescription refilled because his eye was asymptomatic until yesterday.

We diagnosed the patient with a mid-peripheral ulcer secondary to corneal erosion that was precipitated by his most recent Avastin injection. Because the infection was caused by a surgical procedure, we ordered a culture. Additionally, we provided the patient with a sample bottle of Vigamox and instructed him to use the drops every hour while awake and Q3H overnight.

The infection quieted with an aggressive dosing regimen—despite the culture returning positive for fluoroquinolone-resistant *S. aureus*. Fortunately, we did not need to switch him to another medication or employ a sustained-release antibiotic delivery system.

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Guarding Your Patients' Eyes from Harmful Light

Part Two: the Importance of Protection/Prevention

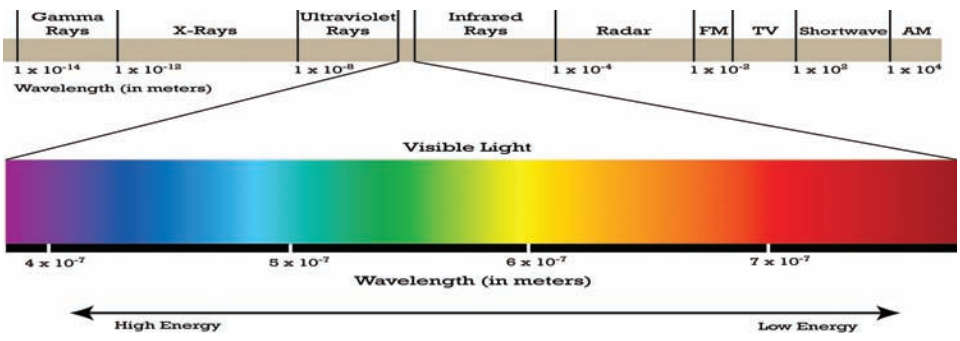
By Ryan Parker, OD

A three-part series about the effects of ultraviolet (UV) and blue light on eye health. Part one served as an educational piece, reviewing the risks and benefits associated with UV and blue light. This month's column looks at how nutrition, reducing exposure and certain lenses play a role in protecting and preventing against the development of age-related macular degeneration. For the next and final part of this series, an engaging point-counterpoint awaits you.

It's a typical Friday afternoon, and my last patient, Mr. Jones, has arrived. It has been three years since his last visit, but as I review his chart, it looks like it will be a routine exam. Mr. Jones is 55 years old and has a family history of cataracts and age-related macular degeneration (AMD). I think to myself, "Let's bump up that add and start the weekend."

I begin the exam, and just as I thought, Mr. Jones needs more add. He sees fairly well at 20/20, but during the fundus exam, I notice a few small drusen. I inform him that his vision has changed and then dive into the macular degeneration risk conversation. I have this talk with my patients on a regular basis, and they usually want to know what they can do to prevent it—especially if they have witnessed a family member go through the disease process. I take this opportunity to explain to patients how they can decrease the risk of AMD progression though ocular nutrition and by protecting their eyes against harmful blue light, one of the key risk factors in retinal cell death and AMD.

As we enter the discussion on prevention and protection against light's harmful effects, we can break things down into three different areas: nutrition and lifestyle, exposure and blue-blocking technology. But first, a quick review on blue and ultraviolet (UV) light.



Understanding Blue Light

UV light is part of the non-visible light spectrum and we are exposed to it any time we are out in the sun. It can cause damage to our eyes, particularly the cornea and the lens. Blue light is part of the visible light spectrum and reaches deeper into the eye. Its cumulative effect can cause damage to the retina and in certain wavelengths, it is implicated in the development of AMD.[1–3] While only 1% of UV radiation reaches the retina in adults, visible blue light easily penetrates to the retina[4] and can cause oxidative stress in both the photoreceptor outer segment and the retinal pigment epithelium.

AMD cases are expected to double over the next 30 years, in part because of the aging of the population. As practitioners, we can do our part to try to keep that from happening by educating our patients about how nutrition and lifestyle, exposure and blue-blocking technology can play a part.

Nutrition and Lifestyle

During the "AMD conversation" with patients, I talk about diet, lifestyle choices and the benefits of nutraceuticals. I have discussed vitamins with patients since I started practicing optometry. Vitamin supplementation increases the antioxidant levels in the retinal cells. I am a firm believer in talking to my patients about formulas that are backed by research, and I routinely recommend an Age-Related Eye Disease Study (AREDS) formulation, anti-oxidative supplement with lutein and zeaxanthin. I stress that these ocular vitamins can reduce the risk of AMD progression by 25% over a five-year period.[5]

I also ask patients about their smoking status and encourage smokers to quit. I also advise them on the benefits of adding leafy green vegetables to their diet.

Patients can also prevent and protect themselves from the harmful effects of UV radiation and damaging blue light by reducing their exposure to them, as we'll discuss now.

Exposure to Blue Light

Because blue light exposure is cumulative, just like UV radiation, we can further prevent disease progression by limiting our exposure. Remember, the sun exposes us to UV radiation in addition to visible light.

Blue light also comes from artificial light sources, which have become increasingly abundant over the past few years. Compact fluorescent lights (CFLs) and light-emitting diodes (LEDs) contain blue light. Many of us have made the switch to these new energy-saving bulbs in our homes and offices, which will cause a rise in blue light exposure, as will the increasing use of smartphones, tablets and laptops.

In 2008, the Paris Vision Institute began ground-breaking research to better understand blue light.[6] This was the first *in vitro* test in the ophthalmic industry to split the visible light spectrum into 10-nm bands to determine which bands of light caused the most damage on swine retinal cells. The results showed that maximum cell damage occurs from 415 nm to 455 nm, with a peak at 435 nm ± 20 nm. This damaging band of light was termed Blue-Violet light. Cumulative exposure to Blue-Violet light will lead to retinal cell death and is a risk factor for macular degeneration. Additional studies have found that not all blue light is damaging.[7] Blue-Turquoise light ranges from 465 nm to 495 nm and is essential for sleep/wake cycles, memory, mood, cognitive performance and pupillary constriction. Blue-Turquoise light is also needed for visual acuity and color perception.

Blue-blocking technology represents another measure patients can take to prevent and protect themselves from the harmful effects of UV and blue light.

Blue-Blocking Technology

Several new products and technologies have been developed to shield our patients' eyes from blue light's harmful effects, including blue light-blocking intraocular lenses for cataract patients and specialized spectacle lenses. The early blue blockers typically featured amber lenses that filtered out 100% of blue light. Today, the traditional melanin-tinted blue blockers, such as BluTech™ (Eye Solutions), have advanced and are designed to protect the eyes from blue light, improve contrast, reduce eye fatigue and maintain color balance. It's important to mention that these lenses contain melanin and deflect 45% of the blue light spectrum. Remember, not all blue light is bad light, so blocking 45% of the entire spectrum isn't ideal. And for some of my patients, the melanin causes a lower visual transmission as well as aesthetic issues.

The newer choice to hit the market is photosensitive No-Glare lenses that incorporate blue-blocking technology. Examples include SeeCoat Blue™ (Nikon), Recharge EX3™ (Hoya) and Crizal® Prevencia™ No-Glare lenses (Essilor).

Crizal Prevencia is my lens of choice when it comes to reducing blue light exposure. This product is superior to its competition because it blocks more of the damaging Blue-Violet light and UV radiation than anything on the market today. Crizal Prevencia has patented technology that selectively filters out harmful Blue-Violet light and UV radiation, including backside UV reflections. Crizal Prevencia also allows beneficial Blue-Turquoise light to pass through the lens while maintaining excellent lens transparency. Crizal Prevencia No-Glare lenses are able to deflect 20% of the harmful Blue-Violet light our patients are exposed to on a daily basis. The Paris Vision Institute's research also showed that this amount of deflection reduced retinal cell death by 25%.[6] No other product on the market currently offers this much deflection. Furthermore, it's a very similar figure to what we expect with AREDS formulations.

Choose Your Weapons

New research on AMD and technologies such as genetic testing, as well as the benefits of different multi-vitamin formulations continue to provide advancements for our patients. I turn to Crizal Prevencia lenses for patients who are frequently exposed to artificial light sources that contain high amounts of damaging blue light, constant users of tablets and smartphones, and those who exhibit early signs of AMD or have a strong family history of macular degeneration. Crizal Prevencia will perform like the other Crizal products you trust. Plus, the lens has an Eye-Sun Protection Factor of 25 and virtually eliminates backside UV reflections. It also features complete protection from the enemies of clear vision: glare, scratches, smudges, dust and water.

Dr. Parker opened Parker Family Vision Center in 2007 after being involved in two partnerships. He is among a select group of optometrists in the state of Oklahoma who have completed the training to become licensed to perform photorefractive keratectomy eye surgery.

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Author's note: My deepest thanks to the hard-working men and women at Essilor for providing our profession with a product that not only delivers exceptional vision, but also protects and preserves those delicate retinal cells.

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PEER-REVIEWED PRA ARTICLE

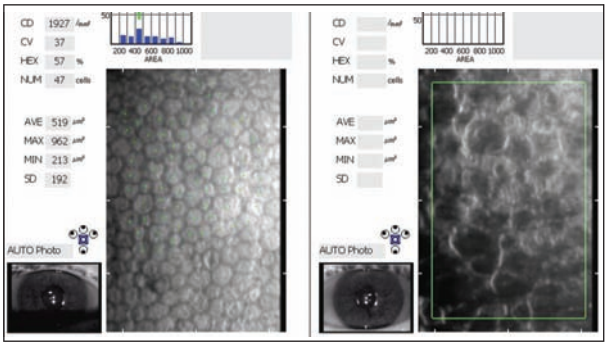
Corneal Disease Report

Endothelial Cell Restoration: Growth or Graft?

Seminal studies in regenerative research could impact the way we treat and manage corneal dystrophies. **By Kathy Kelley, OD, Marianne O. Price, PhD, and Francis W. Price Jr., MD**

Regenerative medicine has been an increasingly successful method to treat disorders of the heart, pancreas and cartilage, but regeneration of the corneal endothelium has yet to reach a comparable stage. The commonly held dogma has long been that dystrophy is a death sentence for endothelial cells, which are notoriously non-duplicating and dormant.

This grim reality has prompted much innovation in surgical interventions to replace damaged endothelium with healthy tissue. In recent years, selective keratoplasties have emerged as a revolutionary approach to the treatment of corneal dystrophies, such as Fuchs'. But only recently have investigators begun to show that regeneration may indeed be possible. Seminal studies in Japan have indicated that corneal endothelial cells may have some proliferative capacity when appropriately stimulated. These researchers have explored the use of rho-kinase (ROCK) inhibitor drops as an alternative to corneal transplantation, which could greatly impact the way we treat and manage corneal diseases.



Images of corneal endothelium in an untreated eye with Fuchs' and one treated with DMEK. At left, the healthy donor endothelial cells form a regular hexagonal pattern. At right, it is difficult to discern viable endothelial cells.

Corneal Dystrophies

The corneal classification system names five dystrophies of Descemet's membrane (DM) and the endothelium—Fuchs' endothelial corneal dystrophy (FECD), posterior polymorphous dystrophy (PPD), congenital hereditary endothelial dystrophy 1 (CHED1), congenital hereditary endothelial dystrophy 2 (CHED2) and X-linked endothelial corneal dystrophy (XECD).[3]

• ***Fuchs'***, the most common corneal endothelial dystrophy, affects up to 2% of the US population. The distribution of the disease varies around the world, and it is typically rare in Japanese individuals. It is a progressive, late-onset, bilateral disease with autosomal dominant inheritance. Females are affected at 2.5 times the rate of males, for reasons that have not yet been elucidated.

Clinically, corneal guttae are the initial manifestation of FECD. These drop-like excrescences project from the posterior surface of DM. In the early stages, the cornea can also have a "beaten metal" appearance with pigment dusting on the endothelium. The guttae initially appear centrally and eventually coalesce. The endothelial cells die, reducing the endothelial cell density. Over time, both the pump and barrier functions become compromised, causing the cornea to swell and lose transparency. As the swelling progresses, epithelial microcysts can form and coalesce to become bullae.

Patients with Fuchs' dystrophy suffer from reduced vision, which is typically worse in the morning due

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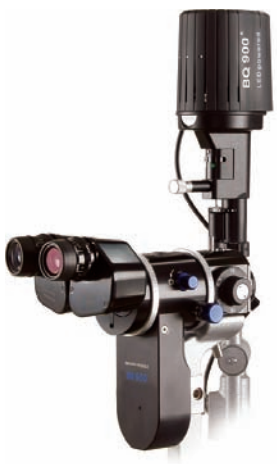

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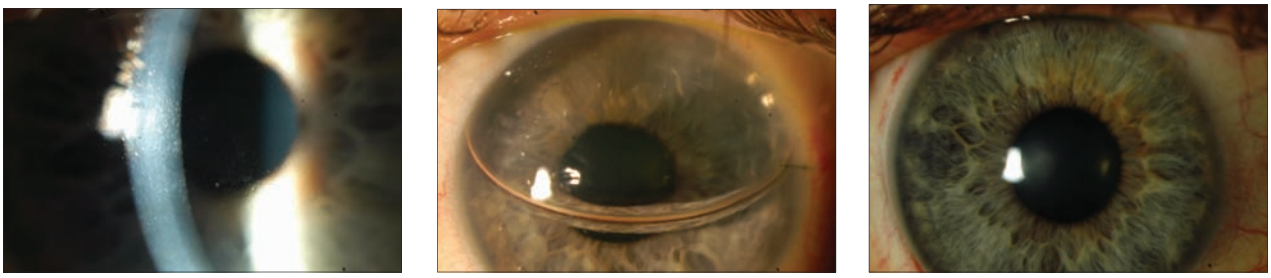

As Fuchs' progresses, the cornea becomes edematous and guttae deposited on DM scatter light (left). One day after DMEK, an air bubble helps seal edges of the newly implanted donor endothelium (center). Two weeks after DMEK, the cornea is clear (right).

to increased stromal edema from overnight hypoxia. Because the guttae scatter light, FECD patients experience glare and photophobia, which can interfere with everyday tasks such as driving. This impairment of daily living activities under bright lighting is often more severe than would be expected based on measurements of visual acuity in a darkened exam lane. In the later stages, patients may experience tearing and pain from ruptured epithelial bullae.[1-4]

• ***Posterior polymorphous corneal dystrophy*** is also a dominantly inherited bilateral disease, but can have an asymmetric presentation. It presents in the second or third decade of life, with most patients being asymptomatic and stable. The abnormalities in PPMD occur at the level of DM and can take on different shapes: vesicle-like lesions, band lesions with a "railroad track" appearance and diffuse opacities.

The presence of vesicular lesions on DM is the hallmark of this dystrophy. Corneal edema is infrequent, but can occur and may be rapidly progressive. Another characteristic of PPMD is peripheral anterior synechiae; these can range from fine adhesions noted only with gonioscopy to large, broad-based membranes. The iris can be uninvolved or may exhibit broad areas of atrophy. PPMD shares similar clinical features with iridocorneal endothelial syndrome (ICE), so careful differentiation is needed. ICE syndrome is often unilateral, progressive and non-familial.

• ***Congenital hereditary endothelial dystrophy 1 & 2*** are bilateral disorders that involve the entire endothelium at birth; the cornea is congenitally cloudy. They are rare, except in Saudi Arabia and southern India.

CHED1 is autosomal dominant, while CHED2 is autosomal recessive, more common and severe. Corneal clouding can range from diffuse haze to a ground-glass, milky appearance. Patients experience blurred vision, often accompanied by nystagmus.

• ***X-linked endothelial corneal dystrophy*** is more common in males. It presents as congenital corneal clouding with a milky ground-glass appearance. The gene mutation has not been identified.

Current Treatment Options

While patients can use hypertonic saline drops to reduce corneal edema during the early stages of FECD, transplantation is the definitive treatment for corneal endothelial dysfunction. In the 20th century, full-thickness penetrating keratoplasty (PK) was the only surgical option, whereas in the 21st century, targeted endothelial replacement through a technique known as endothelial keratoplasty (EK) has supplanted PK procedures. EK is safer and provides faster visual recovery.

Endothelial keratoplasty is performed through a small incision, similar to cataract surgery. The most frequently used technique is Descemet's stripping endothelial keratoplasty (DSEK), which removes the central portion of DM and dysfunctional endothelium and replaces it with healthy DM, endothelium and posterior stroma taken from a donor cornea.[5] The donor tissue is folded or curled for insertion through a small incision, then unfolded and pushed snugly against the back of the patient's cornea with the use of an air bubble in the anterior chamber. This bubble dissipates over four to five days, leaving the DSEK attached. These grafts do not require any sutures, resulting in rapid visual recovery. Most patients can achieve a best-corrected vision of 20/25 to 20/40.

To further improve visual outcomes, progressive corneal surgeons have switched to a newer technique called Descemet's membrane endothelial keratoplasty (DMEK), which replaces a patient's diseased DM and endothelium with healthy DM and endothelium from a donor cornea.[5,6] But in contrast to DSEK, DMEK does not include any donor stromal tissue.

Because a DMEK graft is extremely thin, it can be safely inserted through an even smaller incision than that used for DSEK

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(<2.9mm); smaller incisions are always prized in corneal surgery, as they induce less postoperative astigmatism. Using thinner donor tissue has improved visual outcomes as anticipated—sparing the host cornea from the addition of donor stroma reduces the potential for higher-order aberrations to affect visual acuity. Most DMEK patients achieve BCVA of 20/25 or better.

An unexpected benefit of DMEK is a reduction in the incidence of immunologic graft rejection episodes to less than 1% of cases. Because of the rapid and predictable outcomes and visual improvement with DMEK, surgeons are now able to treat the two eyes of a patient just one to two weeks apart—similar to modern cataract surgery.[7] Corneal transplants have high success rates in patients with corneal dystrophy; five-year survival rates are 90% to 95%.[8,9]

Prospects for Topical Therapy

Is there anything on the horizon for treating diseases like FECD or corneal edema after injuries and cataract surgery without needing a transplant? A signaling molecule that may promote corneal endothelial cell proliferation, migration and adhesion is being investigated as a possible medical therapy for corneal dystrophy. Corneal endothelial cells are generally quiescent and non-replicating in adults; however, recent studies suggest that they do have some proliferative capacity when appropriately stimulated.

The signaling molecule under investigation is one of a family of molecules called ROCK inhibitors. These agents are protein serine/threonine kinases that influence cell migration, apoptosis (programmed cell death) and proliferation. In particular, ROCK signaling is thought to promote cell-cycle progression in various cell types, including corneal endothelial cells, although the underlying mechanism is unknown.

A Quick Refresher

Corneal endothelial cells control corneal hydration to maintain stromal clarity and allow passage of nutrients from the aqueous humor into the cornea.[1,2] In adults, they exhibit little to no regenerative capacity. With normal attrition, cell density decreases from a median of about 3,400 cells/mm^2 in teenage years to about 2,300 cells/mm^2 in the ninth decade of life.

The corneal endothelium secretes collagen that forms DM, which is banded at birth and gradually increases in thickness. The collagen secreted after birth is not banded and can be distinguished as a separate layer by histology.[1,2]

A Japanese team has been investigating the use of this molecule to promote proliferation of cultured corneal endothelial cells. In 2009, Naoki Okumura, MD, and associates found that inhibition of the ROCK pathway with the selective inhibitor known as Y-27632 could promote primate corneal endothelial cell survival in vitro.[10] Primate corneal endothelial cells were harvested and cultured in a medium containing Y-27632 at a 10-µM concentration. It facilitated proliferation as well as adhesion of monkey corneal endothelial cells, and it inhibited apoptosis.

Subsequently, this same team demonstrated that following trans-corneal freezing to kill the central endothelium, injection of cultured endothelial cells along with application of an eye drop containing Y-27632 could regenerate the central endothelium and restore corneal clarity in monkeys. They next demonstrated that trans-corneal freezing followed by application of the ROCK inhibitor eye drops also could restore corneal clarity in monkeys, even without injection of cultured endothelial cells.[11]

In 2013, the same team reported results of the first study in eight human patients—four had central corneal edema and were diagnosed with Fuchs' dystrophy, while the other four had diffuse pseudophakic corneal edema.[11] Trans-corneal freezing of a 6mm area to kill the central corneal endothelium was followed by application of Y-27632 eye drops six times daily and gatifloxacin eye drops four times daily for seven days. Corneal clarity was restored in the four patients with central corneal edema, but not in the four with diffuse corneal edema.[11]

A subsequent paper reported longer follow up of one of the patients treated for Fuchs' dystrophy.[12] The vision in that 52-year-old patient improved to 20/16 and, 18 months after treatment, the endothelial cell density was 1,549 cells/mm^2 centrally and 705 cells/mm^2 peripherally. In early 2014, the Japanese team performed their first injections of cultured endothelial cells into three human eyes, followed by application of Y-27632 eye drops.[13]

These preliminary results have generated much excitement. Clearly, further safety studies are needed because cell proliferation, adhesion and migration normally are tightly regulated throughout the body to help prevent tumors and cancer development. Additional studies are also needed to determine the appropriate dosing strength and duration, as well as the optimal time to intervene in the disease course, especially with Fuchs' dystrophy. The guttae that develop with Fuchs' dystrophy are smaller and less prominent in Japanese eyes than they are in white eyes. Because the guttae scatter light, causing glare and photophobia, a surgical procedure to remove the

guttae would be required in white eyes if the condition had already advanced to the stage of causing corneal edema or glare.

The possibility of a topical treatment for corneal endothelial dysfunction is compelling. Although ROCK inhibitors show promise, further safety studies and larger comparative studies are needed. Endothelial keratoplasty is currently the treatment of choice, providing patients with rapid visual recovery, with DMEK providing the best visual outcomes. ■

Dr. Kelley specializes in cornea and external disease, serving as the principal investigator for dry eye clinical trials.

Dr. Marianne Price is executive director of the Cornea Research Foundation of America in Indianapolis.

Dr. Francis Price Jr. is the founder and president of Price Vision Group and the Cornea Research Foundation of America.

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Corneal Disease Report

Can You Identify These Tricky Topographies?

Early awareness of corneal surface anomalies can help to reveal the nature of the condition—and its treatment. By Jessica Bezner, OD, and Paul M. Karpecki, OD

Employing technology to provide a higher standard of care is foremost in setting the optometrist apart in an ever-increasingly competitive environment. Subtle signs of corneal dystrophies, degenerations and irregularities may be detected with corneal topography at an earlier point than what's possible with the human eye. Furthermore, the ability to show a patient an image or scan is the "hard evidence" that many patients need to better understand their clinical signs. In turn, this leads to a more favorable perception of the provider (you!) and better patient compliance with recommended treatment and follow-up visits.

For patients struggling with limited acuity in spectacles or standard soft contact lenses, a specialty soft or rigid gas permeable lens may make a difference in vision; corneal topography can dramatically aid the evaluation of such patients. This article focuses on the employment of corneal topography relative to ocular irregularities that are present secondary to disease, trauma or surgery.

Mapquest

With the former manual keratometry method, the curvature of the ocular surface was assessed through alignment of two corneal mires (reflections) along the major meridians of the eye (steep and flat). While some corneal irregularities such as poor tear quality or keratoconus could be detected, manual keratometry was limited when compared to today's automated topography.

Advances in current topographers have established the ability to interpret corneal data via maps that illustrate the amount of change over the corneal surface: various types of maps are classified as refractive, sagittal, tangential or elevation. The refractive map provides insight into the change of refractive power across a patient's eye, and is a good way to reveal the focusing power of the eye attributable to the cornea, as well as the magnitude of cylinder present in an astigmatic eye.

Refractive maps are useful when estimating values for LASIK refractive surgery or selecting an intraocular lens implant for cataract extraction.

- *The sagittal map*, also known as an axial map, presumes the change in corneal curvature is relative to a perfect sphere. This normalizes the data and, in turn, results in less accuracy, but is still a good tool to evaluate the course of change across the cornea.
- *The tangential map* is generated by compiling the instantaneous radius of curvature across each of the given points of the cornea. This property is why tangential maps are innately more accurate for evaluation of contact lens selection for scleral or specialty lens fits.[1,2]
- *The elevation map* is typically best to gain an impression of how steep or flat the eye is, and aids in initial lens selection, in particular for scleral or other specialty lenses.

One of the first things to evaluate when looking at a topography image is the elevation map. This provides the "big picture" of the contour of the ocular surface, and quickly identifies what type of surface we are dealing with. This map uses a relative sphere or average sphere to depict the corneal shape. Warm colors represent areas that are elevated above that sphere, and

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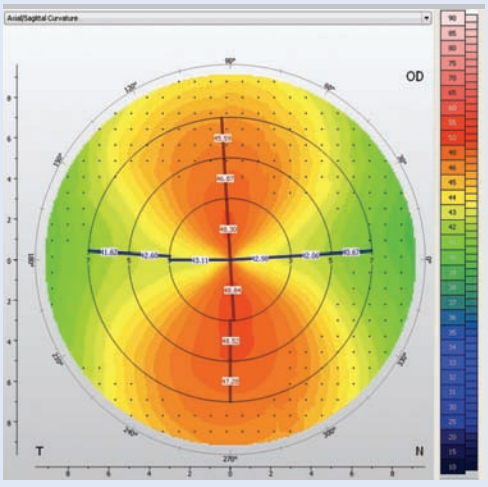
bluer colors represent areas that are lower than a relative sphere.

Another critical, and perhaps most commonly recognized, map is the axial topography, sometimes referred to as a power map. This map is generated from reflections that come off the device's concentric placido rings; it essentially represents the slope of change as one moves from central to peripheral cornea.

The following examples illustrate the correlation between various corneal etiologies and topography maps. Compare the map and slit-lamp images found throughout this article with the descriptions below.

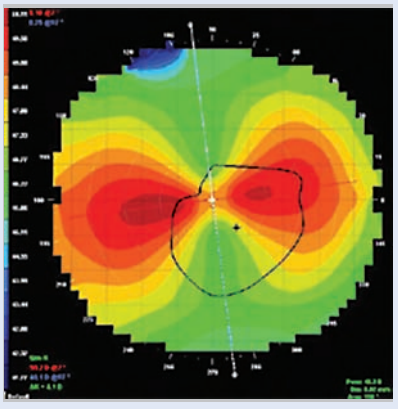
1. With-the-Rule Astigmatism

The example shown here represents the most common topographical image observed in patients with astigmatism. The with-the-rule pattern refers to a refractive axis at 180° (e.g., -2.00 -3.00 x 180) and the warmer colors (faster slope of change) represent the steeper drop in power related to astigmatism.



2. Against-the-Rule Astigmatism

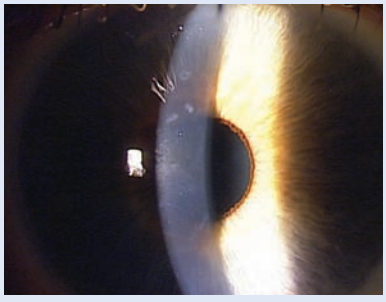
This less common form of astigmatism is represented as a horizontal bowtie, as observed here, resulting in a refractive error in minus-cylinder form in the 90° axis.

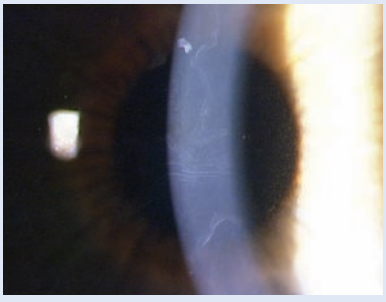


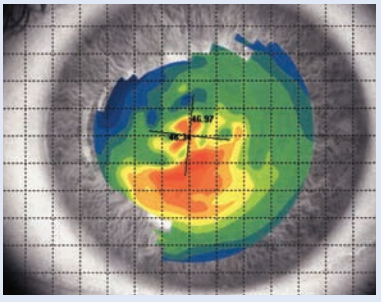
3. Epithelial Basement Membrane Dystrophy

In this axial curvature map, you can observe the irregularities in the superior cornea, which are consistent with the slit-lamp image representing areas of map-dot-fingerprint dystrophy. The difference from the center to the area of greatest irregularity is about 1.50D to 2.00D. Because it is close to the visual axis, a change of this magnitude often is sufficient enough to decrease visual acuity.

There is no exact dioptric change that would correspond to visual compromise, as it depends on the pupil size, the magnitude, the location and numerous other variables. But it can at least outline the areas of involvement for patient education, and perhaps allow the clinician to consider a surgical procedure such as a superficial keratectomy of phototherapeutic keratectomy.







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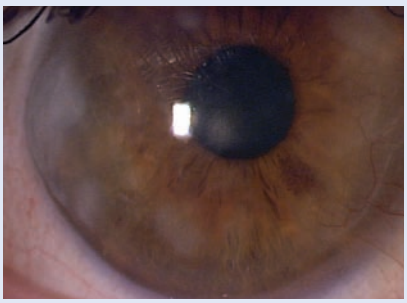
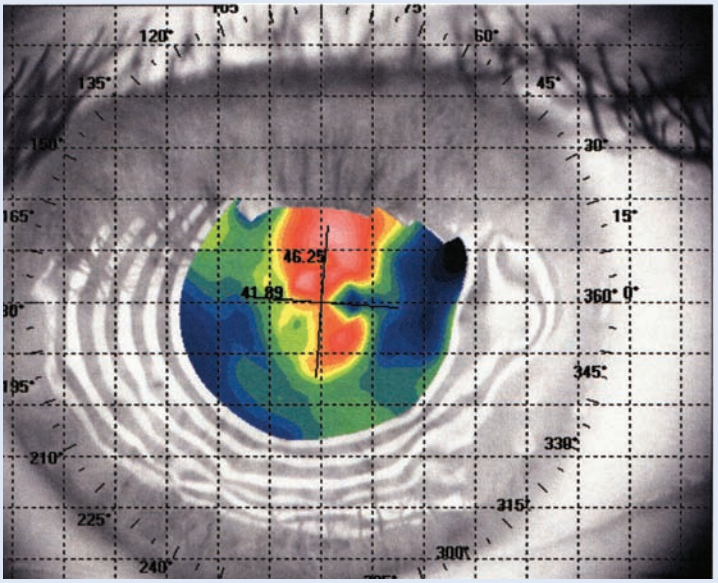
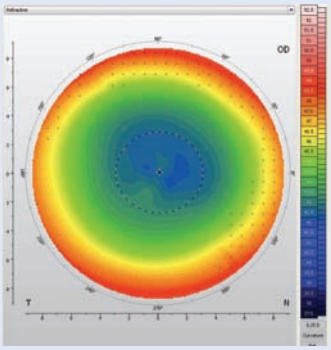




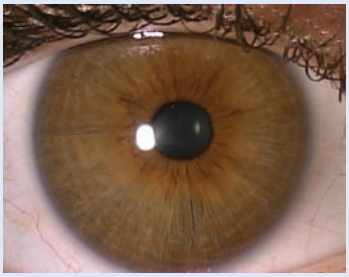
4. Salzmann's Nodular Degeneration

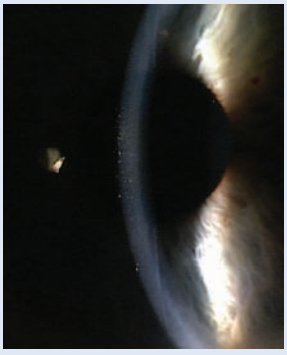
In this example, one can clearly see the corresponding nodules present in both the photo and topography. The level of irregularity, including more than 4.00D of cylinder, is also noted. The elevation map would best represent the actual nodules, although an axial topographical map would show the level of irregularity caused by these entities.

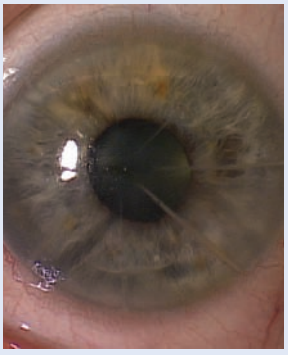


5. Corneal Ectasia, Post-LASIK

Corneal flattening seen subsequent to LASIK is easily detectable on a topography map. The cooler colors represent a flatter curvature that is consistent with the treatment zone of the laser procedure. Patients with myopic regression often request contact lenses to restore their visual acuity. Some can be fit in a standard soft lens, but most require a specialty lens to reflect a much flatter base curve.

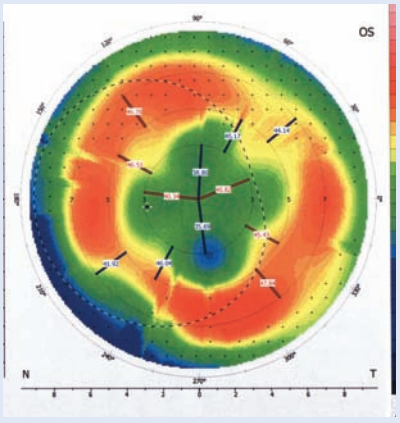






6. Corneal Ectasia, Post-Radial Keratotomy

More often than not, patients who have undergone RK need to be fit into a specialty lens with a rigid optical zone to restore quality of vision. This topography example directly highlights the areas of flattening in a patient with a history of four-incision RK. Often, scleral lenses are employed in this type of patient to completely vault over the flattened cornea.



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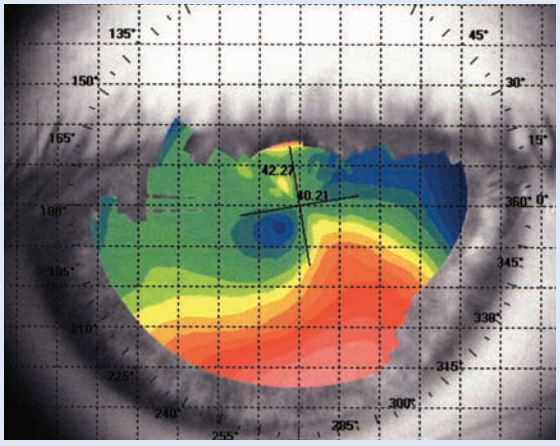
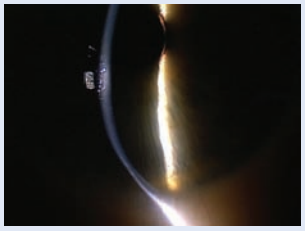


7. Keratoconus

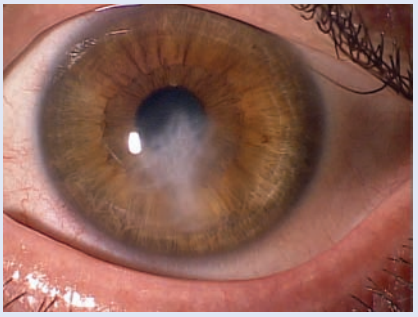
This condition is likely the most common entity that comes to mind when people think of the clinical value of corneal topography.[3] The key to making this diagnosis is to observe the inferior steepening. The keratometry readings (Ks) or power changes in the inferior cornea are typically 1.40D or more than the central Ks; this can be observed with axial topography.[4] The elevation maps will show a much higher area above a reference sphere in the inferior cornea.

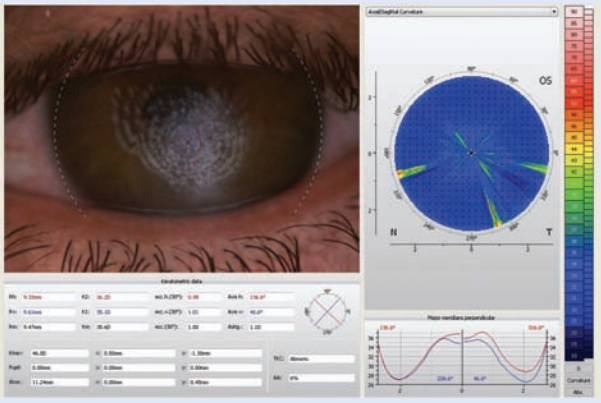


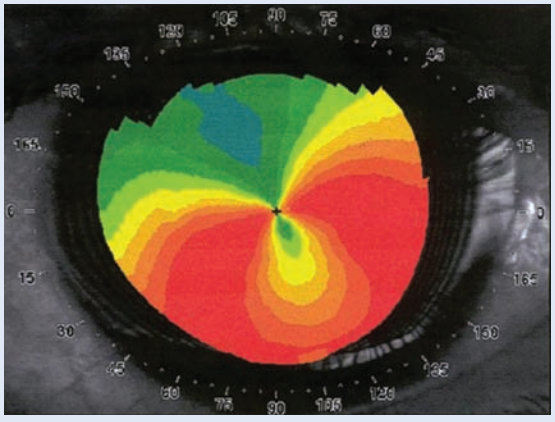
Keep in mind that, in patients (especially younger ones) who present with unstable refractive error, an increase in astigmatism of one eye over the other, or a loss of best-corrected visual acuity, will manifest on topography. Again, the most common appearance will be an inferior steepening.

8. Advanced Keratoconus

In this case, thinning of the cone's apex led to corneal hydrops, resulting in severe scarring that topographic imaging had a difficult time detecting—a comparatively rare instance in which the condition is better observed at the slit-lamp than in the topography map.

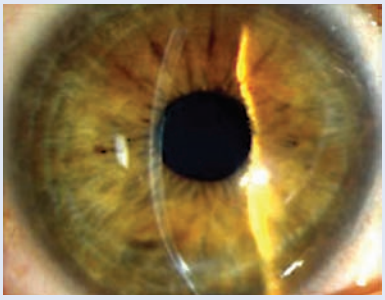






9. Pellucid Marginal Degeneration

This condition is similar to keratoconus except that the more peripheral inferior cornea is involved in pellucid marginal degeneration. Both are ectatic, progressive conditions. The "classic" sign of PMD is known as a "crab claw" or "kissing birds" (although this pattern can also be present at some stages of keratoconus). It represents far peripheral steepening with superior flattening.



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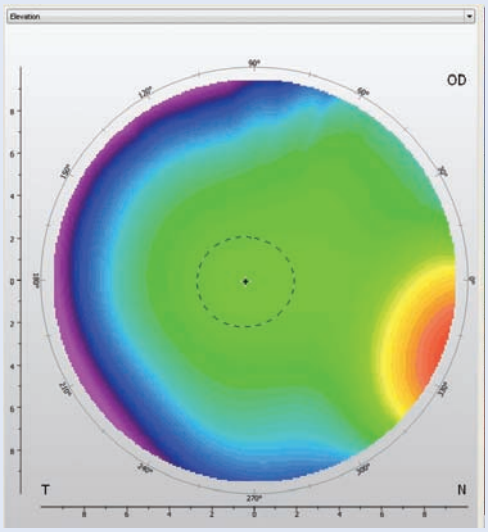
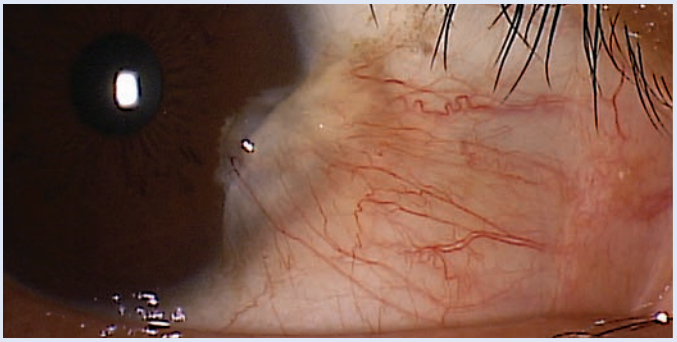
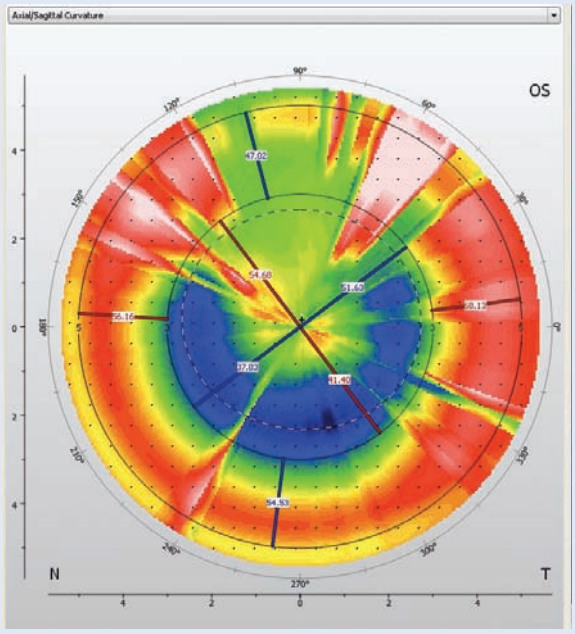
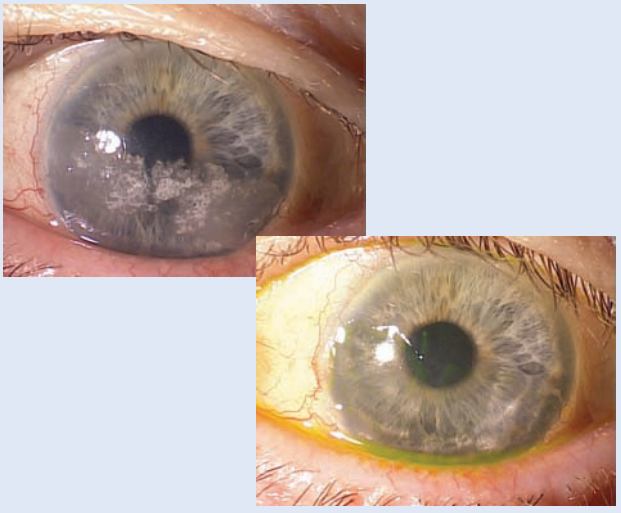


10. Pterygium

The local area of steepening noted here at 5 o'clock is due to the presence of a pterygium that was beginning to encroach into the cornea. This patient's scan was performed as part of the preoperative evaluation for removal of the pterygium.







11. Band Keratopathy

Here, topography was attempted prior to removal of the band keratopathy, but was not possible due to distortion from the thick band of calcium present in the cornea. Interestingly, following a keratectomy for removal of the band, this patient's topography revealed a flattened area (blue) along the path of the keratectomy.

Drs. Bezner and Karpecki practice at Koffler Vision Group in Lexington, Ky.

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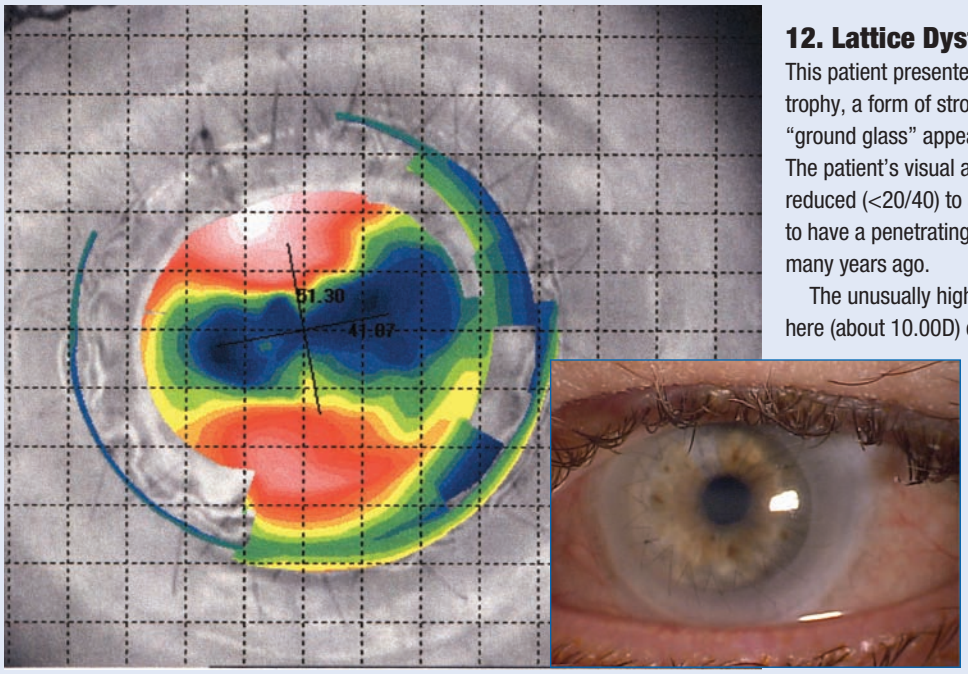
3. Caroline P, Andre M, Kinoshita M. Etiology, Diagnosis, and Management of Keratoconus: New Thoughts and New Understandings. Pacific University College of Optometry. Available at: www.pacificu.edu/optometry/ce/courses/15167/etiologypg4.cfm. Accessed March 4, 2014.
4. Himanshu M, Swarup R. Imaging modalities in keratoconus. Indian J Ophthalmol. 2013;61(8):394-400.



12. Lattice Dystrophy

This patient presented with bilateral lattice dystrophy, a form of stromal dystrophy resulting in a "ground glass" appearance and cloudy cornea. The patient's visual acuity in the right eye was reduced (<20/40) to a degree that he had elected to have a penetrating keratoplasty (PK) of that eye many years ago.

The unusually high amount of cylinder shown here (about 10.00D) occurs in corneal graft patients because the corneal surface is highly irregular in nature due to the PK graft. These patients typically rely on a specialty lens to recreate a smooth optical front surface of the eye that does not distort the entering light rays upon entering the eye.

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Corneal Disease Report

The Pathogens of Corneal Infection: Know Your Enemy

A multitude of organisms threaten the integrity of the cornea. Learn their secrets and you'll be better prepared to mount a robust defense. By Aaron Bronner, OD

If you know your enemies and know yourself, you will not be imperiled in a hundred battles; if you do not know your enemies but do know yourself, you will win one and lose one; if you do not know your enemies nor yourself, you will be imperiled in every single battle.

—From *The Art of War* by Sun Tzu, military strategist, ancient China

With an estimated 30,000 cases per year in the United States, microbial keratitis is not an uncommon source of corneal blindness or vision loss.[1] Looking at the indications for keratoplasty, one can see that infection, either as scars or in their active form, account for about 8% of all transplants.[2] The serious nature of these pathologies is not the only feature that gives us pause, however. The deceptively tidy title of "microbial keratitis" can lead a person to believe that, regardless of etiology, this broad family of conditions progress along a pre-set continuum from early to severe disease. This, unfortunately, is false.

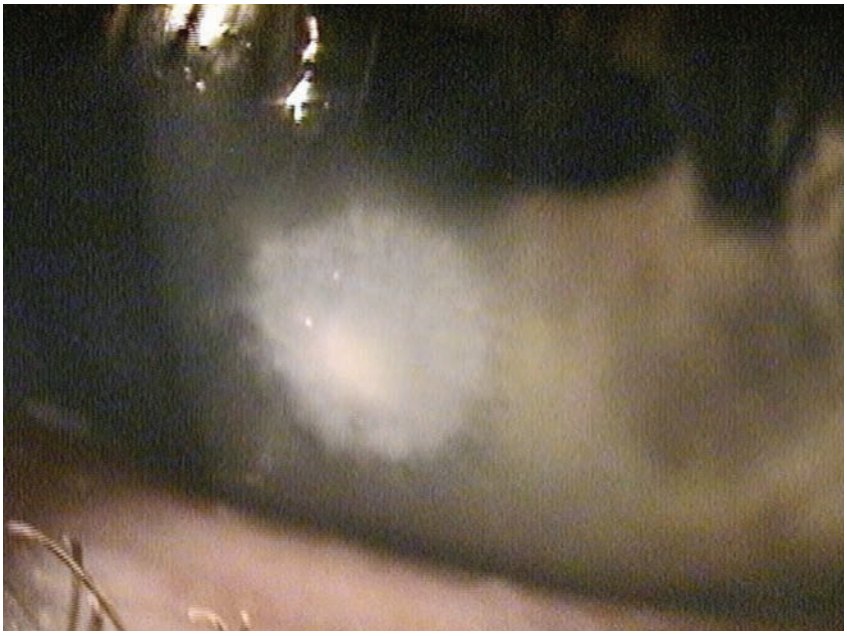
The spectrum of disease caused by corneal infection varies widely, based on host characteristics, treatment factors and, obviously, infectious etiologies. Various corneal pathogens cause rapid and widespread tissue destruction and perforation. Others cause relatively indolent infections that do not generate symptoms until the cornea has already been widely colonized. The virulence, relative rate of progression and collateral tissue damage seen in different infectious organisms owes much to the specific etiology's structure and behavior. The purpose of this review is to analyze the important sources of ulcerative corneal infection, consider how they cause pathology and assess treatment options available to manage these various conditions.

A Bug's Life

The sequence of bacterial infection involves (1) bacterial adhesion to a surface; (2) invasion, or breakdown of tissue to allow bacterial spread; and (3) colonization or replication. As routine as they may seem, the passive barrier functions provided by the ocular surface are dramatically effective at preventing corneal infection by limiting bacte-

Release Date: April 2014
Expiration Date: April 1, 2017
Goal Statement: Infectious corneal ulcers are sight-threatening events that require careful attention by the clinician. This course reviews many microbial sources of ulcerative corneal infection—their life cycles, clinical manifestations, and how they how they cause pathology—and also assesses treatment options available to manage these various etiologies.

Faculty/Editorial Board: Aaron Bronner, OD
Credit Statement: COPE approval for 2 hours of CE credit is pending for this course. Check with your local state licensing board to see if this counts toward your CE requirement for relicensure.
Joint-Sponsorship Statement: This continuing education course is joint-sponsored by the Pennsylvania College of Optometry.
Disclosure Statement: Dr. Bronner has no financial relationships to disclose.



Staphylococcal corneal ulcer, characterized by a round, gray and dry-appearing infiltrate.

What Gram Staining Does—and Doesn't—Reveal

This simple means of classifying organisms has little to do with their pathologic capacity. In reality, it is of more use in microbiologic taxonomy.

The difference between a gram-positive result and gram-negative one is a function of the organism's cell wall structure; specifically, how that cell wall either traps dye (gram-positive) or is susceptible to decolorization (gram-negative). Acid-fast organisms, such as *Mycobacterium* species, stain poorly as gram-positive.

Though gram-stain patterns are not inherently linked to pathogenicity, they do have clinical relevance when selecting appropriate antibiotic treatments.

rial adherence. A combination of factors—such as the lacrimal fluid flow, the blink reflex, the mucin-associated apical surface of epithelial cells and the antimicrobial proteins found in the tear film—all contribute to a rate of bacterial keratitis that is extraordinarily low when one considers the abundance of micro-organisms on the ocular surface.

Normal ocular flora are able to be cultured or identified with polymerase chain reaction on analysis of the tear film, lids and conjunctiva in a high percentage of all eyes.[3,4] In one study, *Staph.* species, the most frequently encountered ocular pathogens, were present on the ocular or periocular tissue in 96% of eyes.[3] Despite this near-constant microbial bombardment, bacterial corneal ulcers have a relatively low estimated prevalence of 10/100,000 in the US.[5] It's well defined that very few bacterial species—namely, the gram-positive *Corynebacterium diphtheria* and *Listeria monocytogenes* and the gram-negative *Haemophilus aegyptius*, *Neisseria gonorrhoeae* and *Neisseria meningitides*—have the potential to adhere to and penetrate an intact epithelium.[1] Fortunately, all are relatively rare ocular pathogens.

The typical sources of bacterial keratitis (i.e., *Staphylococci*, *Streptococci* and *Pseudomonas aeruginosa*) all require some compromise to the epithelium to initiate the infectious process, as they can adhere to the edges of the defect but not to the apical epithelium itself. In industrialized countries, the primary risk factor for development of microbial keratitis is soft contact lens use, accounting for up to 65% of all cases in the US.[6,7]

Trauma is the most frequently encountered risk factor in non-industrialized countries and remains an important risk among patients of first-world countries as well. Traumatic cases of microbial keratitis are also more likely to involve atypical organisms, such as fungi, *Nocardia* and nontuberculous mycobacteria.[1,8,9]

Ocular surface disease severe enough to create corneal compromise is the third most important risk factor for bacterial keratitis.[6,7]

Though the risks can be organized at this level to help the clinician in creating a differential diagnosis, the underlying issue is likely the same for all three risk factors: compromise to the corneal epithelium, which allows adherence of the typical corneal pathogens. Once adherence to a defect takes place, however, the process of infection is underway. The subsequent clinical ulceration is then a result of etiologic and host factors.

Gram-positive Organisms

Staphylococcus species are gram-positive cocci and exhibit multi-dimensional growth patterns; thus, their colonies have a grape cluster-like appearance upon staining. They are typically believed to be commensal; that is, they are inherently neither symbiotic nor pathogenic, and only cause disease in opportunistic settings. *Staph.* species are the dominant organisms of the normal ocular and periocular flora.

Depending on the particular study cited, they are either the most or second-most common etiology in infectious ulcers.[1,7,10,11]

Staphylococcal corneal infections are typically seen with round or oval, creamy, dense infiltrates and an overlying epithelial defect. They do not generate the stromal necrosis seen with *Pseudomonas* infection. Surrounding cornea may occasionally be edematous and the anterior chamber may have significant sterile reaction, with manifestations of cells, flare or hypopyon. The coagulase-negative group, primarily *Staphylococcus epidermidis*, may generate a mildly symptomatic, indolent infiltrate in an arborizing pattern known as infectious crystalline keratopathy (ICK).

Both *Staph. aureus* and *Staph. epidermidis* have exhibited a pattern of antibiotic resistance. These specific colonies—generally referred to by their historic names methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE)—account for a large percentage of staphyloccal-associated eye infections. While methicillin is no longer used as an antibiotic, these strains often exhibit resistance to a number of other, conventional antibiotics, leading to difficult-to-treat infections.

MRSA has traditionally been described as a nosocomial, hospital-borne illness; however, beginning in the 1990s, a community-acquired variant of MRSA (CA-MRSA) has since emerged. CA-MRSA seems to exhibit less resistance than hospital-acquired disease, but a greater virulence profile.[12]

Streptococcal species are a family of polar-dividing, chain-forming gram-positive cocci. The most frequently seen ocular pathogen of this group, *Strep. pneumoniae*, is also the most frequently encountered cause of corneal infection in the developing world.[5] While not a dominant component of the normal ocular flora, *Strep. pneumoniae* is part of the normal flora of the nasopharynx, and thus is unsurprisingly linked to keratitis associated with dacryocystitis.[1,13,14]

The clinical picture of streptococcal species varies from with mild indolent infection, occurring at one end of the spectrum, to severe cases at the other.[1,14] The infiltrate generated is typically round, with an overlying epithelial defect initially, but develops creeping, serpiginous characteristics and can quickly lead to perforation. As with *Staph.* corneal ulcerations, sterile anterior chamber reaction culminating in hypopyon is a common finding.[1,14,16] Both *Strep. pneumoniae* and its fellow alpha-hemolytic group relative *Strep. viridans* may produce ICK under appropriate, immune-suppressed conditions.[15,20]

Gram-negative Organisms

Pseudomonas aeruginosa is a gram-negative rod that causes opportunistic, acute and severe corneal disease. It is the most frequently encountered gram-negative cause of corneal ulceration and, in certain tropical settings, may be the most common overall.[1,17]

Microbiology Terms Demystified

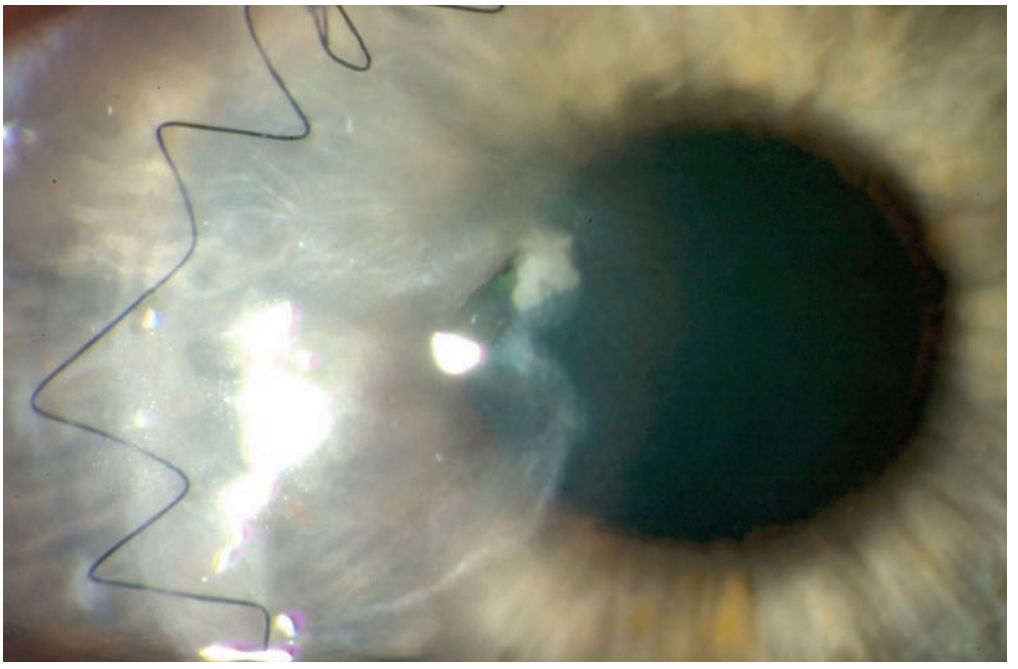
Many words used in microbiology sound familiar to us, but their precise meanings may be unclear. Below are some common terms related to corneal infectious disease. Although these are not universally agreed upon definitions, they can be used as a general guide.

- **Pathogenicity:** The ability of an organism to generate disease in a host. A highly pathogenic species may be able to infect a non-compromised host, whereas an organism with lesser pathogenicity would require some form of compromise to the host tissue; the latter is a so-called opportunistic pathogen.[57]
- **Virulence:** The magnitude of disease an organism may cause in a host. A highly virulent pathogen causes severe disease presentations, and a weakly virulent pathogen produces mild disease. Virulence factors of specific pathogens are features of the organism that enhance its ability to cause disease.[57]
- **Indolent:** Refers to a slow-growing pathogen that establishes colonies gradually. Indolent infections often cause few symptoms while they are establishing their presence. Despite their absence of aggressive and rapid tissue destruction, indolent infections often have poor prognoses due to delayed treatment, as patients often do not seek care until they become symptomatic. This delay leads to well-established colonization of the organism and greater difficulty in its eradication.
- **Fastidious:** Refers to micro-organisms with very specific environmental demands necessary to support growth, such as *Neisseria* and *Haemophilus*. Chocolate agar is used to select out for a number of fastidious species.
- **Biofilm:** A complex colony of bacteria encased in an extracellular polymeric substance (EPS), or glycocalyx. These bacteria exhibit cell-to-cell communication and some degree of specialization depending on the level they occupy within the biofilm, making their behavior quite different from that of the traditionally recognized "planktonic" or free-floating solitary form of bacteria.

Biofilms are sometimes logarithmically less susceptible to antibiotics, even those determined effective through culture and sensitivity. This is because sensitivity testing assesses only the planktonic version of the pathogen, not the EPS-encased biofilm version. Biofilms have been implicated in cases of infectious crystalline keratopathy (ICK), which may explain this presentation's relative recalcitrance to therapy.[54]

Pseudomonas species become more common in the setting of contact lens use. Its presence in bacterial keratitis among non-contact lens users is 5% to 17%, but can be the causative agent in up to 40% of keratitis cases involving soft lens wearers.[1,7]

The clinical appearance of *P. aeruginosa* is that of a rapidly progressive, suppurative, necrotic stromal infiltrate with an overlying epithelial defect. The ulcer is classically described as "soupy" in appearance, and may emit a sweet odor. Sterile hypopyon often accompanies the keratitis.



Nontuberculous *Mycobacterium fortuitum* complex corneal ulcer to a graft. Note the granular, waxy appearance with uneven, ill-defined margins.

Clinically, the disease progresses rapidly, with perforation likely in cases of delayed or ineffective treatment. Virulence of the organism is owed partially to the proteases and exotoxins it produces. These features accelerate its course, leading both directly and indirectly (via the immune response) to stromal destruction, and may propagate clinical progression even with effective antibiotic therapy.[23]

Pseudomonas infections are also relatively unique among bacterial species, given their propensity to form ring infiltrates—a characteristic of viral, fungal, protozoan and atypical bacterial infections—and are the only pathogen other than *Mycobacterium leprae* and *Acanthamoeba* which has been shown to generate clinical perineuritis.[1,18-20] As in all cases of ring infiltrate formation, the lesion is theorized to represent an antibody-antigen precipitate to the various toxins produced by the organism. There is no clear rationale for the rarely described perineural infiltration. Conversely, the course of *Pseudomonas* keratitis may rarely be superficial and non-aggressive, with prominent corneal epithelial vesicles.[1,20] This presentation may be tied to the organism's ability to replicate within the basal epithelial layers.[23]

Serratia marcescens is another family of gram-negative bacilli, which, like *Pseudomonas*, are linked frequently to contact lens wear (more commonly seen with GP lenses than soft lens wear). *Serratia* species are saprophytes, i.e., they consume decaying material, and are opportunistic pathogens. Most studies report *Serratia* as the second-most frequently occurring gram-negative source of keratitis, behind *Pseudomonas*, but at least one study reports it as the more frequently occurring pathogen in the setting of contact lens use.[24]

Ulcers caused by this group have shared features with *P. aeruginosa*; namely, a necrotic corneal ulcer, thinning and progression to perforation. Hypopyon formation is possible, though not a hallmark of infection.[25] Similarities in clinical appearance with *Serratia* and *Pseudomonas* may be linked to the similar proteases that both organisms produce, allowing rapid and widespread tissue destruction.[23,25]

Atypical Bacteria

Nontuberculous *Mycobacterium* and *Nocardia* species are atypical etiologies of bacterial keratitis. They are both technically acid-fast, and stain variably as gram-positive. Like *Serratia* and fungi, these organisms are typically saprophytes. In both cases, trauma involving organic matter or metallic foreign bodies is the primary risk factor, accounting for up to 90% of cases.[40] The reason for the greater association with trauma compared to more typical organisms is twofold: these groups are not part of normal flora, and they have widespread distribution in soil.

Sizing Up an Infiltrate

Though most infectious corneal infiltrates present as round or oval lesions and generate a fairly broad differential list, cases of branching or dendritiform keratopathy appropriately bring herpes simplex virus (HSV) to mind. It's important to consider, however, that while HSV is the primary cause of infectious dendritiform keratopathy, it is not the only one. The conditions below may also be included in a differential diagnosis of branching corneal lesions.

Infectious

- Herpes simplex virus—ulcerative, unilateral.
- Varicella zoster virus—non ulcerative, unilateral.
- *Acanthamoeba*—non-ulcerative, unilateral pattern epitheliopathy may be the most common early manifestation of the disease.

Non-infectious

- Thygeson's SPK—Not typically dendritiform, but may occasionally coalesce into branching lesions; non-ulcerative, may be unilateral or bilateral.
- Corneal verticillata—bilateral whirling, non-ulcerative.
- Systemic tyrosinemia—bilateral; often young when first discovered, may be paired with mental retardation.
- Post-penetrating keratoplasty epithelial hypertrophy—history of PK, non-ulcerative.

A key point to remember: of all sources of dendritiform keratopathy, HSV is the only truly ulcerative condition; all others would be more appropriately described as epitheliopathies. Therefore, while others may produce a patchy fluorescein pattern, HSV dendrites will stain brightly. Whether the lesion is unilateral or bilateral also should help in differential diagnosis.

As sources of keratitis, neither are common, each accounting for 1% to 1.5% of infectious corneal ulcers in temperate industrialized nations, but they do have clinical appearances and behavior unique enough to warrant a brief discussion.[40,41]

Nontuberculous *Mycobacterium* keratitis (NTMK) is an indolent infection characterized by minimal symptoms early in the infectious course, with dramatic exacerbation as the disease becomes widespread. The infiltrates have may have an unusual, focal, waxy or "cracked windshield" appearance, and may develop satellite lesions or a ring infiltrate. Early in its course, the keratitis may be totally devoid of inflammation. Prognosis for NTMK is guarded due to its resistance to most antibiotics.

Nocardia keratitis is, likewise, an indolent infection that produces unusual patchy or wreath-like stromal infiltrates with pinhead-sized dense opacities. Alternately, it may mimic the feathery margins seen with fungal infections in a high percentage of cases.[42] Given the strong link with trauma, *Nocardia* keratitis (as well as NTMK) should always be paired with fungal keratitis as part of the differential in cases of unusual infiltrates with a history of trauma. Despite often requiring fortified amikacin in its treatment, the prognosis for *Nocardia* keratitis is actually superior to most other forms of bacterial keratitis.[55]

Treatment Considerations in Bacterial Keratitis

Community practice for suspected bacterial keratitis within general ophthalmology is generally non-culture driven "empiric" treatment, relying on a broad-spectrum antibiotic. In most cases where the infiltrate is small, non-central and superficial, empiric strategies appear to be as successful as culture-driven treatments.[44] In cases where the ulcer is deep, central or large, or the infiltrate exhibits unusual characteristics, full culture and smears (or referral for these services) improves outcomes.[43-45] Even if cultures are taken, initial treatment will almost always be empiric, as culture results can take several days.

The broad-spectrum, fourth-generation fluoroquinolones moxifloxacin, gatifloxacin or besifloxacin are great, commercially available starting points with good action against most common and even some atypical pathogens. Older generations of fluoroquinolones have better gram-negative coverage than gram-positive efficacy. Even with the newer agents, however, fluoroquinolone resistance has been emerging over the last two decades, with perhaps only 15% to 30% of MRSA strains being susceptible to this class.[46]

For fortified agents, cephalosporins generally have a stronger mechanism against gram-positive organisms, aminoglycosides are generally more effective against gram-negatives and the glycopeptide vancomycin is better against gram-positives. A broad-spectrum, fortified antibiotic therapy should include two antibiotic agents, each with different coverage patterns.

The expected clinical response of bacterial keratitis to appropriate antibiotic therapy depends on the etiology, but in general is one of stunted or halted progression of the disease course over the first day and gradual improvement thereafter. Any infiltrate that continues to worsen over a few days' time should lead the clinician to consider alternate diagnoses or treatments.

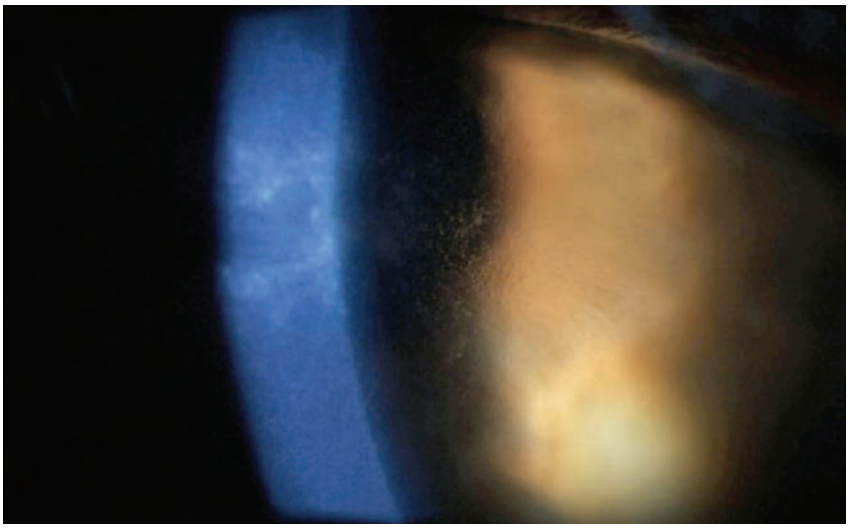
Keep in mind that in vitro sensitivity testing efficacy is not equivalent to in vivo efficacy; thus, concentrations may need to be manipulated with compounding.

Protozoa

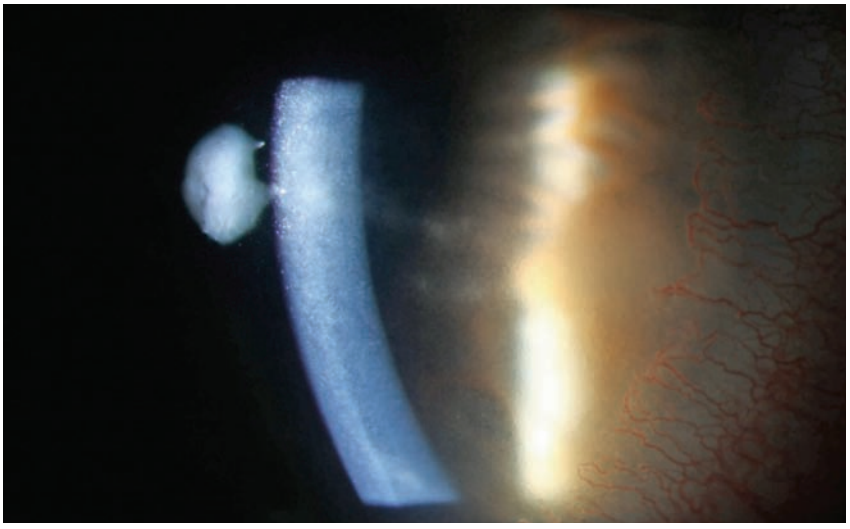
Acanthamoeba is a genus of free-living, ubiquitously distributed protozoa that may rarely cause severe corneal infection. Not inherently pathogenic, *Acanthamoeba* typically feed on blue-green algae, bacteria and fungi. The organism exists in two distinct metabolic states: trophozoites and cysts. When food sources are plentiful and the environment is suitable, the active trophozoite predominates. During periods of environmental stress, the organism may encyst. Cysts are resistant to heat, ultraviolet radiation and lack of food, and may remain viable in this state for years. The organism readily excysts when exposed to a food source.

Humans routinely come into contact with *Acanthamoeba* organisms with no consequence, demonstrable by the fact that nearly 100% of adults carry immunoglobins to the organisms and up to 24% of people who have exposure will exhibit colonization of the nasal mucosa without developing any form of disease.[21,22] As with bacterial keratitis, the primary risk factor in the United States for developing *Acanthamoeba* keratitis (AK) is soft contact lens use, with silicone hydrogel materials being the highest risk type.[28]

Once in the cornea, keratocytes seem to be the organism's primary target.[27] Again, as with bacterial keratitis, an intact epithelium presents a barrier to infection that may be overcome via microtrauma associated with contact lenses. AK is characterized by greater pain than its clinical signs would suggest, although this is not always the case.



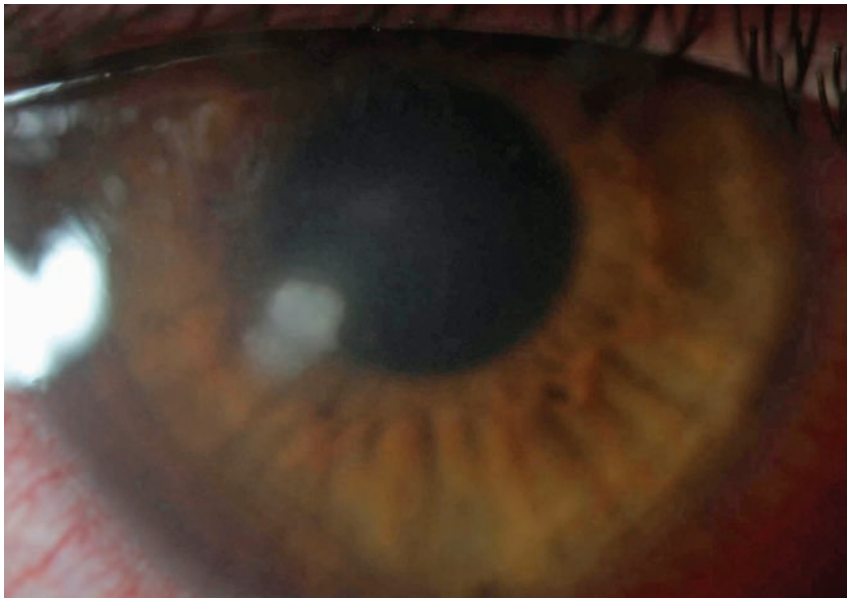
Mild irregular/pattern epitheliopathy in a case of early *Acanthamoeba* keratitis.



Perineuritis finding associated with *Acanthamoeba* keratitis.

Clinically, findings of AK seem to present along something of a continuum. In early stages, the prominent finding is cystic, dendritiform epitheliopathy, and is frequently misdiagnosed as herpes simplex. An epithelial defect is typically not present in very early disease. Mid-stage findings include a ring infiltrate and classically perineural infiltration. It is speculated that corneal nerves present a path of least resistance for the organisms to migrate along. Manifestations late in the disease course may include corneal thinning, perforation, opacification and extracorneal effects such as sterile hypopyon[21,22,26-28]

While the clinical signs in AK are shared with several other pathologies, findings significantly more common in AK than in bacterial or fungal infections include a ring infiltrate (nine to 11 times more likely), dendritiform epitheliopathy (three to six times more likely) and perineuritis (300 times more likely); their presence should generate appropriate levels of clinical suspicion.



Fungal keratitis: A small, non-specific infiltrate with mildly irregular borders. Significant migratory white blood cells give the rest of the cornea a "powdery" appearance.

"The first step to diagnosing AK is to suspect it," Kristin Hammersmith, MD, noted in a review of the condition. Using the diagnostic clues it presents with can be very helpful.[28,30]

• ***Treatment considerations.*** While most anti-amoebic therapies are effective against the trophozoites, cysts are decidedly more resistant to eradication. Therefore, the primary consideration to assess in the treatment of AK is the cysticidal capacity of the proposed therapy. The biguanides polyhexylmethylene biguanide (PHMB) 0.02% and chlorhexadine 0.02% both show very good ability to eradicate cysts, with dosed concentrations 100 times greater than the minimum cysticidal concentration (MCC).

Next-tier treatments are diamidines: propamidine isethionate 0.1% (Brolene, May & Baker) and hexamidine 0.1%, which are active against trophozoites but less active against cysts, and therefore are not acceptable forms of monotherapy.[38]

The primary hurdle to effective use in *Acanthamoeba* keratitis therapy is availability. There are no commercially available anti-amoebics in the US. PHMB and chlorhexadine can be compounded. Interestingly, propimidine is available over the counter as Brolene in parts of Europe and can be ordered online through Amazon.com; again, Brolene is not acceptable monotherapy and would need to be combined with a compounded agent. Of course, any online acquisition of medication is unusual and requires appropriate patient consent.

Treatment of *Acanthamoeba* keratitis is often prolonged, and may continue for several weeks to months after resolution of clinical signs to ensure full eradication of encysted organisms. Due to this prolonged treatment, a toxic keratitis to the medications, particularly the diamidines, may occur.

Fungi

Fungal organisms are a class of eukaryotes that may be unicellular yeasts or multicellular filamentous molds. Their typical food source is decaying organic material, though some species have pathogenic potential. Fungi may be minor components of the normal ocular flora and generally cause disease under opportunistic settings, again relying on epithelial compromise to create infection.[20,33]

Historically, fungi were a rare etiology in infectious keratitis in the US. Additionally, yeasts (such as *Candida* species) were more common in temperate zones, and molds (such as *Fusarium*) were more common tropically. Recently, however, this pattern seems to be shifting. Fungal keratitis appears to be becoming more common in industrialized temperate nations, even after correcting for the two-year spike in 2004-06 as a result of outbreaks associated with contact lens solutions; the filamentous groups also seem to be predominating across all climate zones.[34]

Contact lenses also appear to be playing a more prominent role in the disease process. Though ocular trauma was once the primary risk factor for fungal keratitis, it is currently only responsible for an estimated 10% to 20% of cases of fungal keratitis in the US, whereas contact lens use is reported 20% to 35% of the time.[31,34,35]

The clinical picture of fungal keratitis is varied and non-specific, which may contribute to the poor outcomes associated with it. One study found that, upon presentation to a cornea clinic, roughly 87% of patients were originally misdiagnosed and treated for bacterial or viral keratitis.[35]

Classically, fungal keratitis involves patchy, grayish infiltrates with feathery margins and satellite lesions. While most cases are associated with an epithelial defect, fungal keratitis stands in stark contrast to bacterial keratitis in its ability to deepen the infection, even penetrating to the anterior chamber despite an intact epithelium, lead-

ing to penetration without perforation. Hypopyon and endothelial plaques are frequently described, and an immune ring may develop.

• ***Treatment considerations.*** The treatment course of fungal keratitis is often described as prolonged, and many times will be unsuccessful. This is due to the ability of fungal infections to worsen with an intact epithelium, and to the poor penetration of topical antifungal drugs.

Of all options, topical natamycin 5%, a polyene, is the only commercially available topical antifungal. Natamycin is particularly active against molds and has been the historic treatment of choice for sources of keratitis like *Fusarium* or *Aspergillus*. It may be reasonably employed as monotherapy, in most of these cases. The newer triazole agent, voriconazole, may be compounded for use topically at 1% concentrations, and shows superior efficacy against yeasts, such as *Candida*, and may be as good or superior to natamycin 5% against molds as well.[34,36]

Again, owing to the poor epithelial penetration of antifungals, treatment of fungal keratitis without an epithelial defect should include epithelial debridement to enhance tissue concentration.[20,33]

Viral Infections

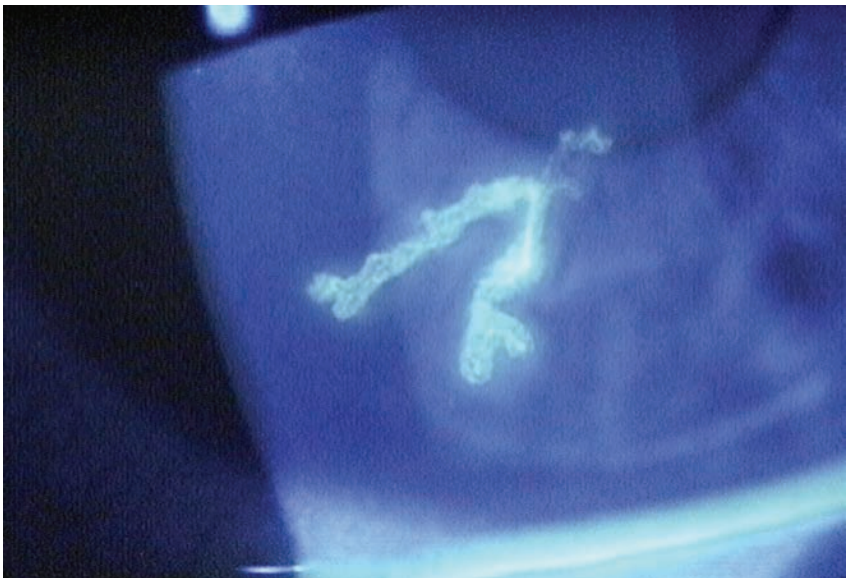
Because viruses are not widely considered to be living organisms, viral infections are somewhat different than the other forms of infection described thus far. This distinction is made due to the lack of a cell membrane, metabolic ability and ability to self-reproduce. Regardless, viral infections are significant causes of vision loss, with herpes simplex infection (and its sequelae) constituting the number-one source of infectious vision loss in the United States.

Though other groups of viruses will cause routine ocular surface disease with occasional resultant inflammatory keratitis, the herpesvirus group is the only viral cause of infectious ulcerative keratitis. This group, made up of several infectious species, is classified as DNA viruses; they exhibit the shared ability to develop latency. The three most important members of this group as it relates to corneal disease are herpes simplex 1 (HSV1), herpes simplex 2 (HSV2) and varicella zoster (VZV). Of these, only the herpes simplex group routinely causes ulcerative keratitis.[48]

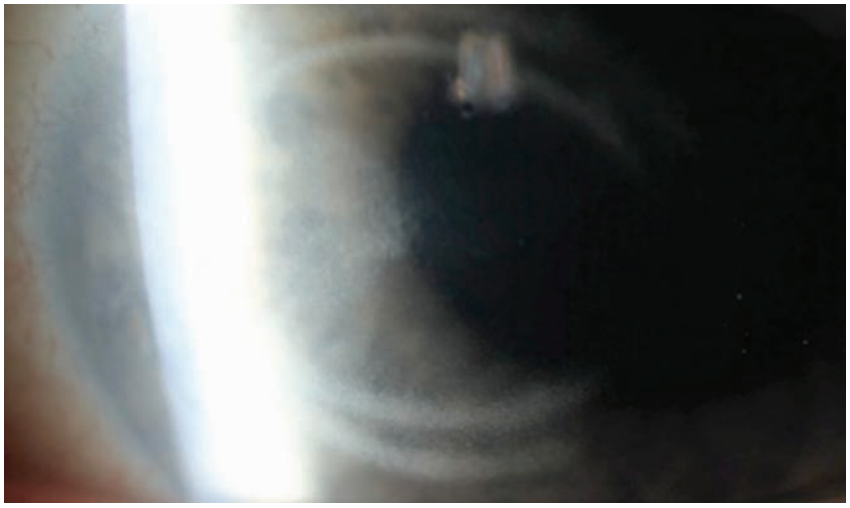
The typical clinical appearance of ulcerative viral keratitis is the dendrite, a lesion so well recognized and defined that no elaboration is needed in this context. Viral sources of non-dendritic corneal ulceration are fairly limited and are related to atypical presentations of herpes simplex virus.

A brief word about necrotizing stromal keratitis is warranted, however, as this manifestation of the disease is easily mistaken for other forms of infectious keratitis. Necrotizing stromal keratitis is an unusual stromal ulceration rarely associated with HSV keratitis. It manifests clinically as a necrotizing infiltrate with thinning that may progress to perforation underlying and epithelial defect—in other words, it mimics the appearance of other forms of microbial keratitis. There is considerable debate about whether this necrotizing stromal keratitis an antigenic inflammatory reaction to viral antigens or an actual propagation of herpetic infection into the stroma.[20,29] While herpes zoster does not cause necrotizing stromal keratitis or true ulcerative dendrites, its corneal infection can give a similar-appearing "pseudodendrite," which represents swollen, infected epithelial cells. These are readily differentiated from true dendrites by their lack of central ulcerations.

Beyond infectious ulcerations, both VZV and HSV may result in ocular surface neurotrophy and its associated chronic recalcitrant epithelial defects without infiltration or infection.[29,48] Just as challenging to treat and sight-threatening as infectious epithelial keratitis, HSV and VZV both also frequently cause immune stromal keratitis.



The classic appearance of a herpes simplex dendrite.



Double corneal immune ring secondary to herpes zoster ophthalmicus. The slight haze at the center of the lesion represents the epicenter of antigen spread, while the ring represents antigen-antibody complex precipitate.

Varivax and Zostavax: Where Do They Fit In?

Prevention of varicella zoster, in both its forms, has been accomplished by the development of two related vaccinations.

• ***Varivax (Merck)*** is given to infants to reduce primary infection (varicella), typically with good results. The vaccine is a live, attenuated virus; the Oka strain is injected in children 12 to 35 months of age. This virus is much more readily contained by the immune system than the wild type, and allows development of adaptive immunity, generally without precipitating severe disease. Varivax has been dramatically successful and has reduced the incidence of varicella in at-risk populations by 70%.[48,51,52]

There are possible consequences to administration of this vaccination, however. Primarily, the impact of future development of herpes zoster within immunized patients is unknown. Some speculate that widespread vaccination may actually increase the rate of herpes zoster, at least in the short term. Theoretically, people who have latent wild-type VZV infection will see a reduction in their normal environmental exposure to VZV. This in turn will reduce immune boosting to the virus that accompanies these exposures.[51] Over time, however, as the attenuated strain—which is more easily contained by systemic immunity—widely replaces the wild strain as the type held in latency, zoster incidence should decrease.[53]

• ***Zostavax (Merck)*** is a booster immunization given to patients to reduce their risk of developing shingles. It is made of the same modified virus as Varivax, but is given at a higher dosage level.

Thus far, it seems logical that Zostavax is perhaps best suited for patients who have an elevated risk of shingles but not an immediate history of the condition. Why? Because a recent episode of shingles would provide the same, and possibly even better, immune-boosting effects as the vaccination. Nevertheless, a previous history of shingles does not contraindicate a booster of Zostavax, which may still be beneficial. Exactly how much protection a booster confers in such cases probably relates to the timing of vaccination relative to the episode; again, the more recent the episode, the less benefit one should likely expect from the booster.

Though Zostavax's effect in herpes zoster ophthalmicus (HZO) may be able to be extrapolated to some degree based on its use in generalized shingles, there are currently no clear guidelines for its role in preventing recurrent HZO.

These manifestations are thought to represent an inflammatory response to non-viable viral antigens found within the cornea. Depending on the infectious etiology of HSV or VZV, this may take the form of nummular keratitis, disciform endotheliitis, interstitial keratitis, ring infiltrates and corneal mucous plaques, and can generally be differentiated from the infectious forms by an intact epithelium.

• ***Treatment considerations.*** Treatment of herpesvirus infections relies on nucleoside analogs: acyclovir, valacyclovir, penciclovir, famciclovir, ganciclovir, trifluridine and ioxuridine. All of these target and block viral replication within infected host cells. Treatment of HSV infectious keratitis may be accomplished with oral acyclovir (or its prodrug forms), debridement of dendritic edges (the reservoir of virus) and/or topical antiviral therapy. A Cochrane analysis of these options shows that topical treatments are equivalent to oral therapies, and that debridement may be a useful adjunct to add to either antiviral approach.[49]

A few historic distinctions exist between the treatment of HSV and VZV infections. First, whereas topical trifluridine is effective treatment in HSV, it is ineffective against VZV. The latter is susceptible to topical acyclovir and other guanosine analogs but, as these have been only available in their oral forms in the US, effective antiviral treatment for VZV has been limited to oral administration only.

Recently, however, a topical formulation of the antiviral drug ganciclovir 0.15% (Zirgan, Bausch + Lomb) has been shown to have some efficacy against both HSV and VZV, giving us another weapon to use against both infections.[50] Second, one result of the Herpetic Eye Disease Study (HEDS) was the routine use of oral acyclovir

at suppression-dose levels in HSV keratitis. While effective in reducing recurrence of both infectious and inflammatory sequelae of HSV keratitis, no large study supports the use of suppression dosing for VZV keratitis. Though one report on immune-suppressed cancer patients showed a positive effect of suppression, it is difficult to extrapolate this data to a normal, immune-competent population.[56]

The use of topical corticosteroids is generally contraindicated in cases of infectious epithelial keratitis caused by herpes simplex infection. These are, however, important components of the clinical armament of the immune stromal keratitis manifestations or herpetic disease; when used, they should be given with topical or oral antiviral prophylaxis.

Although microbial keratitis can be intimidating when first encountered, good outcomes are possible in most cases with appropriate medical intervention. As Sun Tzu said, "know your enemy and know yourself." Though his advice concerned dealing with rival nations rather than infectious disease, in the high-stakes setting of microbial keratitis, it remains good advice today.

Having a basic understanding of the pathophysiology of the different etiologies can allow better correlation between the clinical picture and diagnostic considerations, and can support your efforts to individualize the treatment plan. Just as importantly, understanding yourself—your comfort levels and competence with these cases—can help to guide your treatment and referral patterns to ensure the best outcome for your patients. ■

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

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OSC QUIZ

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1. Which step of bacterial infection does a break in the corneal epithelium permit?
a. Adherence.
b. Colonization.
c. Biofilm development.
d. Replication.

2. Which of these bacterial species cannot penetrate an intact epithelium?
a. *Corynebacteriurn diphtheria*.
b. *Listeria monocytogenes*.
c. Methicillin-resistant *Staph. aureus*.
d. *Neisseria gonorrhoeae*.

3. Which of these is the PRIMARY risk factor for developing fungal keratitis in the US?
a. Prior keratoplasty.
b. Contact lens use.
c. Vegetative trauma.
d. Ocular surface disease.

4. Which of the following is true regarding gram staining patterns?
a. Gram-negative species are inherently more pathogenic.
b. Gram-positive species are inherently more pathogenic.
c. Gram-negative species trap crystal violet dye.
d. Gram-positive species trap crystal violet dye.

5. Which is NOT true regarding staphylococcal corneal infections?
a. Staphylococcal corneal infections typically generate rapidly deepening necrosis.
b. Staphylococcal organisms are the primary source of bacterial keratitis in the US.
c. The infiltrate seen with staphylococcal keratitis is typically round or oval.
d. A hypopyon in staphylococcal keratitis is often a sterile anterior chamber response rather than a sign of intraocular penetration of the pathogen.

6. Which of the following is NOT true regarding methicillin-resistant *Staph. aureus*?
a. Hospital-acquired MRSA (HA-MRSA) preceded the evolution of community-acquired MRSA (CA-MRSA).
b. CA-MRSA is typically more virulent than HA-MRSA.
c. HA-MRSA typically exhibits greater resistance than CA-MRSA.
d. Both CA-MRSA and HA-MRSA are rare and account for a small fraction of all cases of *Staph.*-related eye disease.

7. Which of the following is the most common etiology of infectious bacterial keratitis in the developing world?
A. *Staphylococcus aureus*.
B. *Staphylococcus epidermidis*.
C. *Streptococcus pneumonia*.
D. *Pseudomonas aeruginosa*.

8. Which of the following is NOT true regarding *Pseudomonas aeruginosa*?
a. It is most common in temperate climates.
b. It is typically cited as the most common cause of gram-negative keratitis in the US.
c. Contact lens use dramatically increases its likelihood.
d. Its virulence can at least partially be attributed to endotoxin and proteases it produces.

9. The clinical picture of *Pseudomonas keratitis* includes all of the following EXCEPT:
a. A sweet odor.
b. Widespread stromal necrosis.
c. Temporary worsening of clinical signs even in the presence of effective therapy.
d. An arborizing infiltrate pattern.

10. Which is NOT an infectious sources of radial perineuritis?
a. *Streptococcus viridans*.
b. *Pseudomonas aeruginosa*.
c. *Acanthamoeba*.
d. *Mycobacterium leprae*.

11. Which of the following describes a clinical feature of nontuberculous *Mycobacterium* keratitis?
a. Rapidly progressive.
b. Widespread necrosis of the stroma leading to perforation.
c. Tendency towards antibiotic resistance.
d. Wreath-like infiltrate is classic.

12. The most effective antibiotic against *Nocardia* is generally:
a. Fortified tobramycin.
b. Fortified amikacin.
c. Fortified ceftriazadine.
d. Fortified voriconazole.

13. Which is true regarding efficacy of topical antibiotics?
a. Resistance to fluoroquinolones is rare.
b. Fortified cephalosporins are most effective against gram-positive organisms.
c. Fortified vancomycin is most effect against gram-negative organisms.
d. Fortified aminoglycosides are most effective against gram-positive organisms.

14. Which is NOT true regarding the life cycle of *Acanthamoeba*?
a. They generally feed on blue-green algae and bacteria.
b. They exist in the active trophozoiite form and the metabolically inactive cyst form.
c. The cyst form is resistant to UV radiation and therefore is not susceptible to UV-A riboflavin corneal crosslinking as a treatment.
d. Exposure to *Acanthamoeba* typically leads to clinical infection.

15. Which of the following is a finding characteristic of EARLY *Acanthamoeba* keratitis?
a. Dendridiform epitheliopathy.
b. Ring infiltrate.
c. Perineuritis.
d. Corneal scarring.

16. Which statement is correct regarding the treatment of *Acanthamoeba* keratitis?
a. PHMB 0.02% is available commercially in the US.
b. Chlorhexadine 0.02% is available commercially in the US.
c. Propimadine isethionate 0.1% can be ordered on Amazon.com.
d. Propimadine isethionate 0.1% is the most potent cysticidal anti-amoebic.

OSC QUIZ

17. Which is NOT true regarding fungal keratitis?
a. Over 80% of cases may be originally misdiagnosed.
b. While classic findings are described, in most cases clinical findings are often nonspecific.
c. The disease may progressively deepen even without an epithelial defect.
d. *Candida* species are currently the most commonly involved etiology of fungal keratitis in the US.

18. Which of the following is an effective and commercially available antifungal medication?
a. Brolene.
b. Fumagellan.
c. Natamycin 5%.
d. Voriconazole 1%.

19. Which of the following does NOT produce dendritiform corneal lesions?
a. Herpes simplex virus.
b. Varicella zoster virus.
c. *Acanthamoeba*.
d. *Pseudomonas aeruginosa*.

20. Which is true regarding viruses and the corneal infections they may cause?
a. Herpes viruses share the ability to develop latency within a host.
b. Viruses are widely considered living organisms.
c. Herpes viruses are RNA viruses and as such may be targeted with uracil analogs.
d. Pseudodendrites associated with herpes zoster are true ulcerations of the epithelium down to Bowman's membrane.

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13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
16.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
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18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

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Lesson 110086 RO-OSC-0414

By Pam Lowe, OD, FAAO

Educate Patients About Hydrogen Peroxide Solutions, Reduce Dropouts

CLEAR CARE® Cleaning and Disinfecting Solution for Those Not in Daily Replacement

I tell patients that there is nothing more comfortable than putting a fresh contact lens on every day, which is why I lean heavily toward daily replacement lenses because of the benefits of replacing lenses daily with no possibility of solution complications or poor hygiene/cleaning habits causing complications. *But*, if the patient has high astigmatism, multifocal lenses or overnight needs, then a silicone monthly is the next best option. Since some of my patients still wear contact lenses that require a lens care regimen, I needed to find solutions that delivered similar results to daily replacement. For that reason, I recommend CLEAR CARE®.

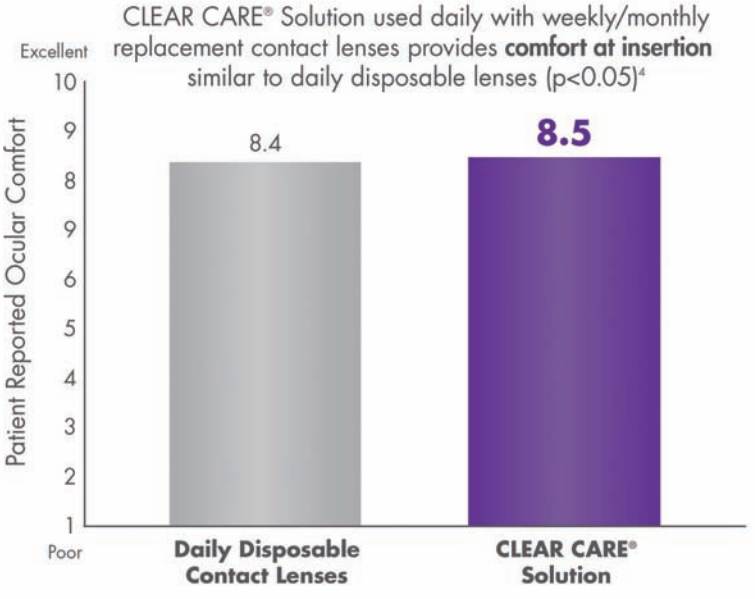
CLEAR CARE® is highly effective for killing pathogens that can be on the contact lens[1-3] and I feel the *best* way to reduce solution-related complications. I believe CLEAR CARE® is the closest way to mimic taking "solutions out of the mix" since after the solution neutralizes, the patient is taking their lenses out of a gentle saline solution, and not exposing the eyes to the preservatives or chemicals found in other solutions. As a result, after disinfection in CLEAR CARE®, contact lenses are left feeling more like new, ocular tissues are not compromised by residual preservative, and wearers experience enhanced comfort on insertion and at the end of the day—very similar to daily disposable lenses (Figure 1).[4] As a matter of fact, in a study of CLEAR CARE® users, 4 out of 5 agreed that cleaning and disinfecting their lenses with CLEAR CARE® got their lenses so fresh, they felt like new.[5]

Prescribe a Branded Lens Care Regimen

The national average for contact lens dropouts is 16%, according to "New Data on Contact Lens Dropouts: An International Perspective" by John Rumpakis, OD, MBA, a study published by *Review of Optometry* in 2010,[6] so it is incumbent that we try to help our patients have the most successful lens wearing experience. Product selection and education is the key.

We are very directive on what lens care systems we want the patient to use. We are certain to educate the patient that other MPS or peroxide solutions are not the *same* as CLEAR CARE®. I explain to patients that they could have sensitivity to the solution they may substitute and that could mean an uncomfortable and inconvenient lens wearing experience. I stress to patients that if they are cleaning lenses they *must* stay with the solution I prescribe. I emphasize that proper cleaning and

Figure 1



Retrospective analysis of 28 contact lens/solution combinations each tests with 40 participants for 3 months with a total of 3,277 participant months. 6 weekly/monthly replacement and 4 daily disposable contact lenses were evaluated. Subjects rated their ocular comfort on a 1 to 10 scale.

good contact lens case hygiene is essential in cutting down on complications and facilitating comfortable contact lens wear. I stress that case hygiene is a must and that reusing any solution is very ineffective for cleaning lenses and may lead to serious eye complications.

Explain Value of CLEAR CARE®

I find that patients who are educated about the benefits of CLEAR CARE® are likely to stay in their lenses long-term and experience high satisfaction with their contacts. As a matter of fact, CLEAR CARE® users are among the most loyal of any lens care brand and are highly satisfied.[7-8]

For peroxide solutions, differences in the case, shorter soak times, the age of the catalytic platinum disc or the solution formulation itself can impact how much residual peroxide is left after neutralization.[9-12] Fortunately, the unique, patented formula of CLEAR CARE® has been designed to balance powerful disinfection with irritant-free comfort. When used properly, CLEAR CARE® leaves behind less residual peroxide after neutralization than the eye can feel—far below the long-established ocular awareness threshold of 100 ppm.[9-13]

CLEAR CARE® has been reco mended by ECPs for years and is the most trusted solution by ECPs.[14-15] I tell patients I am recommending this special system to give them their best lens wearing experience, that there is no substitute to the gold standard cleaning of CLEAR CARE® and that it will help make their lenses feel like new.

Staff being on board with solution-prescribed regimens is essential to a doctor being successful with patient compliance. My staff is well-educated on the key messages needed to make sure patients are educated properly on how to use CLEAR CARE®.

Educate and Promote Compliance with CLEAR CARE®

My patients who use CLEAR CARE® tend to be more knowledgeable about cleaning their lenses and the importance of compliance with cleaning. CLEAR CARE® naturally promotes compliance since it must be used properly otherwise the lenses will give a terrible sting from residual peroxide; because of this, I am extra careful to explain the powerful cleaning properties. I explain that the platinum coated disc in the unique CLEAR CARE® case needs at least six hours to remove an oxygen molecule from H_2O_2, thus creating a gentle saline solution. I emphasize that they don't want to experience what H_2O_2 feels like in the eye, and if they accidently do, they will be *very* motivated to not make that mistake again. We point out the fact that the top of the bottle has a red tip, warning the patient not to put directly in the eye or rinse lens with CLEAR CARE® without putting it through the neutralization process. We also warn that if they *do not* see the familiar "bubbling" immediately after closing the case they must replace the case or clean and rinse the lens with a saline before ever wearing the lenses again.

I strongly prefer daily replacement contact lenses for my patients, but for my patients who still wear contact lenses requiring a lens care regimen, I recommend CLEAR CARE®. I find that patients who are educated by about the benefits of CLEAR CARE® are likely to stay in their lenses long-term and experience high satisfaction with their contacts. For that fresh, out of the pack feeling for my non-daily disposable patients, I trust CLEAR CARE® solution.

> "I find that patients who are educated about the benefits of CLEAR CARE® are likely to stay in their lenses long-term and experience high satisfaction with their contacts. As a matter of fact, CLEAR CARE® users are among the most loyal of any lens care brand and are highly satisfied."

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An Inflammatory Debate

When should you use steroids in patients who present with corneal ulcers? A new SCUT follow-up study may help us understand. **Edited by Joseph P. Shovlin, OD**

Q What do the results of the original SCUT—and the recent follow-up study—mean for clinicians? Have you altered your use of steroids on corneal ulcer patients in light of the results?

A "One of the most controversial areas in cornea and external disease is the use of corticosteroids in the setting of a bacterial corneal ulceration," says ASCRS President Eric Donnenfeld, MD, who practices in Long Island.

Conservative eye care providers have "steadfastly adhered to the policy that no steroids are indicated, due to the risk of exacerbating an existing infection and delaying re-epithelialization," according to Dr. Donnenfeld.

On the other hand, proponents of corticosteroid use believe that the inflammatory process associated with a corneal ulcer is "more visually damaging than the actual infectious process itself," Dr. Donnenfeld says.

Two years ago, with the publication of the Steroids for Corneal Ulcers Trial (SCUT) in the February 2012 *Archives of Ophthalmology*, clinicans got some hard data to help guide clinical decisions. To determine the impact steroid use has on patients with corneal ulcers, SCUT compared prednisolone sodium phosphate 1.0% to placebo in the treatment of corneal ulcers.

The study determined that there was "no difference in three-month best spectacle-corrected visual acuity and no safety concerns with adjunctive corticosteroid therapy for bacterial corneal ulcers."[1] That, however, did not settle the debate.

James Aquavella, MD, professor of ophthalmology at the University of Rochester Flaum Eye Institute, would like to see additional studies conducted before changing his treatment regimen. "Visual acuity and scarring are only one factor to be considered," says Dr. Aquavella. "The intensity and duration of inflammation and the amount (if any) of intraocular response are also important."

According to Dr. Aquavella, the important consideration for clinicians is that the study showed no evidence of worsening in the presence of steroid use. As a result, he says, the clinician has "more flexibility to use his or her judgment."

A follow-up study, published in the February 2014 *American Journal of Ophthalmology*, found that "adjunctive topical corticosteroid therapy may be associated with improved long-term clinical outcomes in bacterial corneal ulcers not caused by *Nocardia* species."[2]

"The take-home message from this study is that corticosteroids may improve outcomes if you know the patient has a conventional bacterial ulceration, such as a *Staph.* or *Pseudomonas* species," says Dr. Donnenfeld. "When the bacterial organism is opportunistic and does not respond readily to conventional antibiotics (e.g., *Nocardia*) corticosteroids can worsen outcomes."

What's worse is that many corneal ulcerations are not bacterial in origin, such as the recent epidemics of *Acanthamoeba* and fungal infections associated with contact lens multipurpose solutions, according to Dr. Donnenfeld. He says adding a corticosteroid under these conditions "can be globe threatening."

In light of these studies, Dr. Donnenfeld currently recommends steroid use "after the infection has been controlled or eliminated in cases where the infection is a classic presentation for a bacterial infection." His treatment regimen differs when dealing with an infection that is indolent, occurs in immunosuppressed patients or those already on an antibiotic, or is secondary to organic trauma. In these cases, Dr. Donnenfeld recommends withholding corticosteroids until the infection is clearly eradicated.

"I traditionally withhold steroids for the first few days, but if inflammation persists at a high level, I will use methylprednisolone 1% and, more recently, difluprednate 0.05% (Durazol)," adds Dr. Aquavella. He also notes that *Pseudomonas* ulceration requires a longer steroid-free period, and any ulceration with fungal involvement will require less steroid use, if any at all.

Additionally, Dr. Aquavella recommends adjuncts such as bandage contact lenses or amniotic membranes, as they can often "mitigate subsequent scarring and the attendant reduction in vision." ■

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Induced Vertical Prism When Prescribing Toric Lenses

Subtle effects of a disparity between eyes may be a factor in patient discomfort

Dr. Hamada is Senior Research Optometrist for Johnson & Johnson Vision Care, Inc. and spent 11 years in private practice prior to joining J&J. Contact her at **whamada@its.jnj.com**.

Weslie Hamada, OD, FAAO

As practitioners, we know the effects of prescribing spectacles with prism, using prismatic light deviation to correct an abnormality in the binocular vision. But unbeknownst to the practitioner, vertical prism can also be present in toric contact lenses, and could result in difficult to describe and often distracting visual disturbances for the patient with monocular astigmatism.

In fact, vertical prism is built into many toric contact lenses by design, as part of the ballasting that keeps the lenses stable. The thicker inferior portion that serves as ballast to align the lens also induces a prismatic effect. A greater thickness differential from top to bottom of the lens results in a greater prismatic effect.

My colleagues and I measured the mean vertical prism present in the optic zone of eight commercially available soft toric lenses. Lenses with BLINK STABILIZED™ Design, including ACUVUE® OASYS® Brand Contact Lenses for ASTIGMATISM and 1-DAY ACUVUE® MOIST® Brand Contact Lenses for ASTIGMATISM, have virtually no vertical prism due to the balanced nature of the design. The other six lenses measured have mean base-down vertical prism ranging from 0.5△ to 1.2△.[1]

Disparity the issue

For patients wearing the same toric lens design in each eye, vertical prism does not pose a problem. Both eyes experience the same degree of image displacement, and the brain adapts easily to fuse the images.

However, a disparity in prism between the two eyes may be problematic. In a study of astigmatism prevalence, 47.4% of subjects with visually significant (≥0.75 diopters D) astigmatism had it in only one eye.[2] Monocular astigmatism is common and, especially now that practitioners are more confident in fitting low astigmats in toric lenses, it is not unusual to find patients wearing a toric lens in one eye and a spherical contact lens in the other.

Most people can tolerate a disparity of up to 0.5△ of vertical prism, but disparities of 0.5△ and higher have been associated with visual discomfort and other symptoms.[3] Individuals with a fragile binocular system, or those who are otherwise more susceptible to visual disturbances, may be more likely to experience new or exacerbated symptoms.[4]

Symptoms and settings†

The symptoms of a vertical binocular vision imbalance may include eye strain or fatigue, headaches, and muscle tension around the eyes. These symptoms are usually subtle; patients may not even associate them with contact lens wear. They can be challenging for practitioners to identify, as well, because they typically don't affect Snellen visual acuity. Rather, vertical prism imbalance may be most bothersome in situations with extreme eye gaze, low lighting, or prolonged near concentration. For example patients may sometimes report difficulty keeping their place while reading.[5]

Uncovering and addressing the need

Contact lens wearers demand a great deal of their visual system for work, school, and even "play," given the contemporary dominance of computers, tablets, and smart phones. Eye strain and headache can have a negative impact on attention and enjoyment.

As with any contact lens wearer—and especially a toric lens wearer—practitioners should always ask careful questions about patients' wearing experience outside the chair. Vertical prism disparity is yet another reason to inquire about "real-world" vision. Do they feel that their eyes are tired or strained, especially in some of the situations described above? Do they suffer from frequent headache or tension in their facial muscles?

Awareness of the potential effects of vertical prism imbalance in creating or exacerbating unwanted disturbances in binocular visual function can be helpful when selecting toric lens designs for monocular astigmats. Particularly for those patients who may be more vulnerable to binocular problems, consider toric contact lenses that offer stability without potential visual disturbances, such as ACUVUE® OASYS® Brand for ASTIGMATISM or 1-DAY ACUVUE® MOIST® Brand Contact Lenses for ASTIGMATISM.

§

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TAKE ACTION IN YOUR PRACTICE

INVESTIGATE

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Do they feel that their eyes are tired or strained? Do they suffer from frequent headache or tension in their facial muscles?

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A lens that reduces or eliminates the possibility of induced vertical imbalance while offering comfort, great handling, UV blocking,* and crisp, stable vision.

EXPLAIN

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†Potential binocular vision imbalance caused by induced vertical optic prism dissociation is a relevant factor for practitioners to consider when fitting toric contact lenses for monocular astigmats or those requiring a mix of toric soft contact lens designs. Clinical studies have not been done to fully characterize the clinical effects of differences in base-down prism among different contact lenses.

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WARNING: UV-absorbing contact lenses are NOT substitutes for protective UV-absorbing eyewear such as UV-absorbing goggles or sunglasses because they do not completely cover the eye and surrounding area. You should continue to use UV-absorbing eyewear as directed. **NOTE**: Long-term exposure to UV radiation is one of the risk factors associated with cataracts. Exposure is based on a number of factors such as environmental conditions (altitude, geography, cloud cover) and personal factors (extent and nature of outdoor activities). UV-blocking contact lenses help provide protection against harmful UV radiation. However, clinical studies have not been done to demonstrate that wearing UV-blocking contact lenses reduces the risk of developing cataracts or other disorders. Consult your eyecare practitioner for more information.

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ACUVUE® BRAND CONTACT LENSES

IOP Rises as Mind Declines

A long-term glaucoma patient with questionable memory and worsening glaucoma slides toward surgical intervention. What went wrong? **By James L. Fanelli, OD**

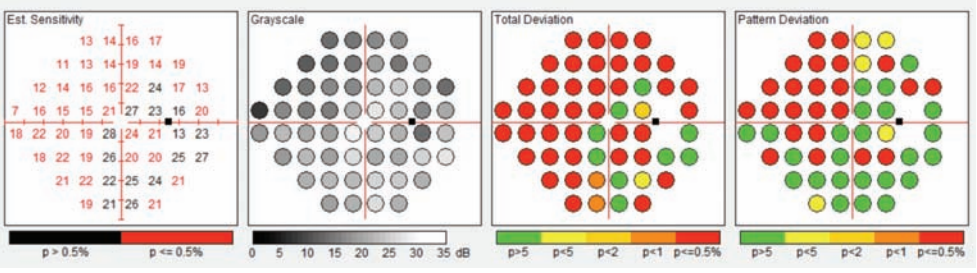
A 79-year-old white female presented to the office in March 2014 following a trabeculectomy in her right eye. She has been a long-term glaucoma patient whom I've seen regularly for the past eight years. Sadly, her decline in cognitive function may very well have contributed to her glaucoma progression.

Patient History

When I first saw her as a new patient in 2006, she presented with complaints solely related to vision. Her systemic medications included Lipitor (atorvastatin, Pfizer), Fosamax (alendronate, Merck), lisinopril, metoprolol and metformin. She was under treatment for diabetes mellitus type 2, which had been diagnosed four years earlier.

At this first visit, her best-corrected visual acuity was 20/20 OD and OS through hyperopic, astigmatic correction. Pupils were equal, round and reactive to light and accommodation, with no afferent defect. Slit lamp examination of her anterior segments was unremarkable. Intraocular pressure measured 26mm Hg OD and 14mm Hg OS. Central corneal thickness readings were 521µm OD and 498µm OS.

Upon dilation, examination revealed exfoliation syndrome in the right eye, with the appearance of characteristic exfoliative material in the anterior lens capsule. Close scrutiny of the anterior segment OD (and OS) revealed no other discernable deposition of this material, in particular along the papillary margin or in the angles. The left eye showed no evidence of exfoliation. Also, her crystalline lenses had minimal age-appropriate nuclear sclerosis, which did not interfere with vision.



This patient's glaucoma was largely under control until her mental status began to decline. Around that time, her visual fields showed an arcuate scotoma and nasal step in the right eye.

Cup-to-disc ratios were 0.40 x 0.40 OD and 0.15 x 0.15 OS; there was no notching or thinning of the right neuroretinal rim that would indicate glaucomatous damage. The retinal vasculature showed mild hypertensive and arteriosclerotic retinopathy OU, which was consistent with her systemic health history. There was no evidence of diabetic retinopathy OU.

Diagnosis

She returned one month later for a complete glaucoma workup. IOP measured 25mm Hg OD and 17mm Hg OS. Standard automated perimetry testing was normal in both eyes. Gonioscopy showed 4+ open angles with minimal trabecular pigmentation OU and no evidence of exfoliative material in the angles. Optic nerve imaging correlated well with the clinical examination of the optic nerve head, as well as the general robustness of the neuroretinal rims OU.

Given the clinical presentation, I diagnosed the patient with exfoliative glaucoma OD and suspicion of glaucoma OS, and prescribed Travatan (travoprost, Alcon) HS OD.

The patient responded nicely to therapy, with post-treatment IOP generally ranging between 15mm Hg and 18mm Hg OD. Visual fields and HRT-III (Heidelberg Engineering) imaging of the optic nerves remained stable.

However, her IOP eventually began to increase. In 2010, I added Alphagan P (brimonidine tartrate, Allergan) to the right eye on a QAM basis. But by 2011, her IOP was steadily rising again, so I increased the Alphagan P to BID OD. Other than gradually increased IOP in the right eye, the neuroretinal rim appearance and SAP field studies had remained

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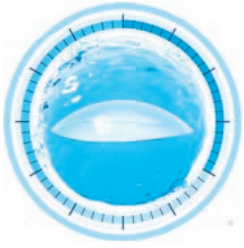

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stable. Throughout this time, the left eye remained unchanged and exhibited no evidence of conversion to glaucoma.

In 2012, we obtained her first Heidelberg Edge Perimeter Flicker-Defined Form (HEP FDF) visual fields, which showed no significant field defects in either eye.

Medication Compliance

Sometime during 2012, I began to notice changes to the patient's affect. All her visits with me had been friendly, cordial and quite interactive. But a subtle change was occurring. Although still smiling and friendly, she left me with the distinct impression that she either no longer fully understood or had lost interest with what was happening with her eyes (and why we were seeing her three times a year).

Furthermore, my ophthalmic technician had made several notes questioning her compliance with the drops; at the completion of each visit, we had to go over very explicit instructions for her medication use (which had continued with Travatan HS OD and Alphagan P BID OD).

By early 2013, her IOP OD was on the rise again, which further concerned me that she was failing to comply with her medication regimen. Also at this time, we noticed slight changes consistent with progression in the neuroretinal rim OD. Visual field testing with HEP FDF confirmed these changes, showing a well-developed arcuate scotoma and nasal step OD. Meanwhile in the left eye, the IOP, fields and neuroretinal rim continued to remained stable.

Once again, we stressed compliance with the medication regimen—but I was doubtful that she would be able to continue without laser intervention. I planned on one more follow-up visit to firm up the need for laser trabeculoplasty in the right eye. Unfortunately, she missed the next several visits due to other health concerns and to issues that I believed were related to her worsening mental status.

When she ultimately returned in October 2013, she'd had an obvious decline in her mental ability. Her historical skills had deteriorated to the point that we were unable to determine her compliance with her medications. Although she was able to carry on a reasonable conversation, she was simply no longer the person whom I met just a few years ago.

She complained of gradually decreasing vision that corresponded to her slowly progressing cataracts, yet she also reported that she was able to drive. By this time, IOP in the right eye had risen to the mid-20s, and the neuroretinal rim and FDF fields showed continued progression.

We were now officially at the point where surgical intervention was necessary.

Surgical Treatment

While laser trabeculoplasty OD was an option, I did not foresee that it would give us a long-term and hopefully medication-free solution to the problem. So, in early December 2013, the patient had combined cataract surgery and trabeculectomy with MMC in the right eye. In January 2014, she underwent lens extraction and IOL implantation in the left eye.

Postoperatively, both eyes are doing remarkably well. Although her post-op medication regimen was a challenge, we were able to enlist the help of her friends and neighbors to facilitate compliance, as she has no family nearby.

At her most recent visit in March 2014, her unmedicated IOP was 14mm Hg OD and 21mm Hg OS. Field testing and HRT-III imaging showed stabilization of the visual field and neuroretinal rim loss. She appears to be fine now (her eyes, at least), and she will likely continue to do well as the bleb is well formed and not inflamed.

Discussion

Even on a good day, with a fully cognizant patient, compliance with glaucoma medications can be a challenge. Add to the picture a patient who is getting older and perhaps more forgetful, and a disease that's highly demanding in its need for control, and you have the perfect setup for a tenuous situation to go bad or get even worse.

What can we do about such a situation? Do we need to move toward surgical intervention sooner in such a case than we usually would? How do we really judge unwillingness to comply against inability to comply, and how do we recognize that?

I don't propose to have the answers. But, having seen this patient for as long as I have, and having gotten to know her, my hunch that she was undergoing a decline in her mental status turned out to be true. Should I have moved her to laser therapy sooner? Perhaps. But, the counter-argument is that everything was going well at that time, so why alter therapy that was working?

The take-home message is, perhaps, that not only do we need to be focused clearly on the status of the neuroretinal rim and visual fields in glaucoma patients, but we also need to be more attentive to the patient's affect, mood and demeanor—as these may be clues to some neurodegeneration elsewhere than the optic nerve. ■

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Two's NOT Better Than One

This patient presented with multiple retinal conditions—one fairly evident, the other not so much. What are they, and which one is more concerning? **By Mark T. Dunbar, OD**

A 69-year-old white female presented with complaints of blurred vision (OS > OD) and difficulty reading. She reported seeing a retinal specialist approximately twice a year for the past three years, and he had told her that there was no treatment for her condition. The patient also informed us that her sister has the same problem and has lost significant vision. Her medical history included controlled hypertension and hypothyroidism.

On examination, her best-corrected acuity measured 20/25 OD and 20/40 OS. Confrontation visual fields were full to careful finger counting OU. Ocular motility testing was normal, and her pupils were equally round and reactive without evidence of afferent defect OU. Her anterior segments were unremarkable. Intraocular pressure measured 15mm Hg OU.

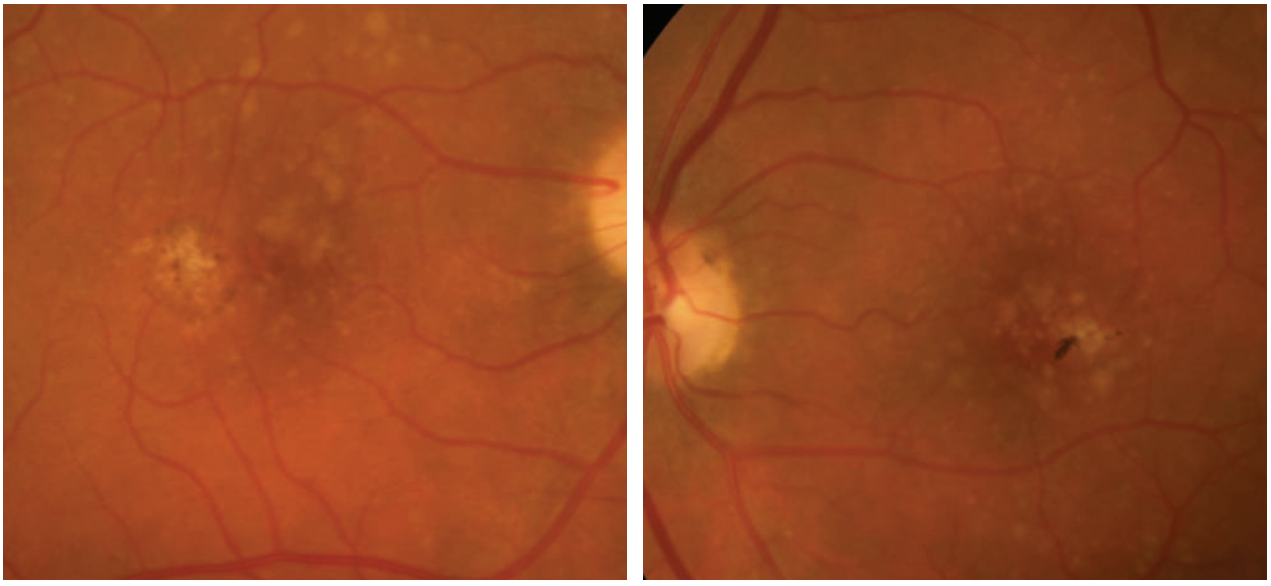
On dilated fundus exam, her optic nerves appeared healthy, with small cups and good rim coloration and perfusion OU. Examination of both maculae revealed obvious changes (*figures 1 and 2*). Additionally, we performed a spectral-domain optical coherence tomography (SD-OCT) scan (*figures 3 and 4*).

Take the Retina Quiz

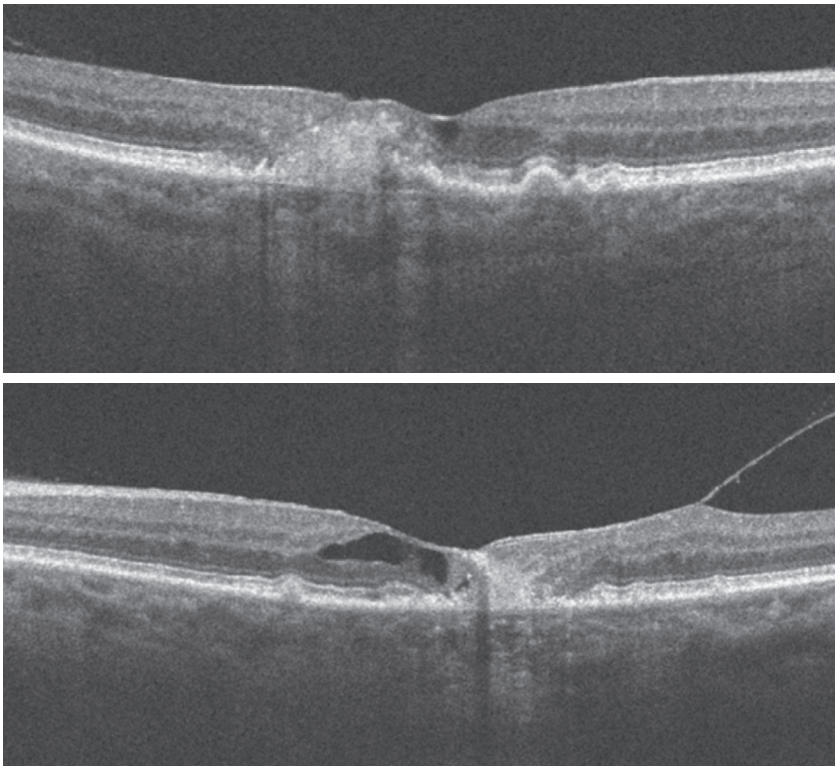
1. What does the SD-OCT scan show in our patient's right eye?
   a. Choroidal neovascularization (CNV).
   b. Cystoid macular edema (CME).
   c. Pigment epithelial detachment (PED).
   d. Scarring and loss of the inner/outer segment (IS/OS) junction.

2. How would you characterize the SD-OCT findings in her left eye?
   a. CNV.
   b. Vitreomacular traction (VMT) with CME.
   c. Internal limiting membrane (ILM) draping and IS/OS junction disruption.
   d. Nonspecific scarring and IS/OS junction loss.

3. Our patient has two diagnoses—but, which is most obvious?
   a. Geographic atrophy of the retinal pigment epithelium (RPE).
   b. Age-related macular degeneration (AMD).



1, 2. Fundus images of our patient (OD left, OS right). Note the retinal whitening around both maculae.



3, 4. The SD-OCT scan of our patient revealed significant changes in both eyes (OD top, OS bottom). What do you notice?

c. CME.
d. VMT.

4. What is the other diagnosis?
a. Macular telangiectasia (MacTel).
b. Bull's eye maculopathy.
c. VMT with CME.
d. Stargardt disease.

5. How should she be managed?
a. Observation.
b. Anti-VEGF therapy.
c. Intravitreal Jetrea (ocriplasmin, ThromboGenics) injection.
d. Pars plana vitrectomy and membrane peel.

For answers, turn to page 112.

Discussion

At first, it appears that our patient has dry AMD. And indeed, that is true. There are obvious drusen present in both maculae and posterior poles, in addition to significant RPE mottling OU. But upon closer inspection, there is more going on than just AMD.

In the left eye, we noted a plaque of pigment hyperplasia located temporal to the macula. Further, the retinal veins within this area appear blunted, or abruptly truncated. We also documented a retinal vein branch located along the superior temporal arcade OS that approached the macula and then stopped suddenly. The vessel made a right-angle turn, heading deeper into the retina. There were similar retinal vein changes in her right eye, as well.

These findings are characteristic of macular telangiectasia. We confirmed the diagnosis via SD-OCT, which revealed a bilateral ILM drape (OS > OD).

Previously, MacTel was termed "juxtafoveal retinal telangiectasia" until the condition was reclassified in 2006.[1-3] There are two primary types of MacTel: type one is known as macular aneurismal telangiectasia (MAT), and type two is known as macular perifoveal telangiectasia (MPT).[3] Our patient has the MPT type.

Patients with MAT typically fall within the parameters of congenital retinal telangiectasis, or Coats' disease. These patients are more likely to exhibit profound vascular changes, with more obvious aneurismal dilations and prominent cystic changes within the macula.

MPT patients usually have a central lamellar cyst with an overhanging retinal drape. In fact, such draping observed via SD-OCT is now considered diagnostic for this condition. Additionally, patients with MPT experience a loss of retinal transparency, smaller and subtler telangiectatic changes within the capillaries, and RPE changes that may precipitate CNV in advanced disease stages.

The SD-OCT scan of our patient's right eye was of particular interest, because it revealed a dense, localized area originating at the level of the RPE that extended into the sensory retina. Here, there was complete loss of the IS/OS junction. This represents a focal area of fibrous tissue, perhaps from an old CNV. Fortunately, it was located just temporal to the fovea, which explained why her visual acuity still measured 20/25.

In the left eye, we also noted an IS/OS junction disruption, as well as incidental vitreomacular adhesion (not traction). These changes, in conjunction with the ILM draping, were responsible for the 20/40 visual acuity.

Unfortunately, there are no

effective treatments for MacTel. Following its reclassification in 2006, a multicenter clinical trial was developed to further explore its pathogenesis and determine any potential genetic links.[3]

A cohort of 400 participants were enrolled and followed annually. After five years, the researchers determined that patients with MacTel had a significantly higher prevalence of systemic conditions associated with poor vascular health—including hypertension, diabetes and coronary disease—compared to those in the control group.

Interestingly, the data indicated that familial transmission occurred in just a small proportion of people with MacTel. The disease inheritance was consistent with an autosomal dominant pattern, but with reduced penetrance.[4] Subsequent genome-wide linkage analysis has identified a single peak with a multi-point LOD score of 3.45 on chromosome 1 located at 1q41-42 in a dominant model.[5]

We explained these findings to our patient, and instructed her to return to her retinal specialist as directed for routine observation.

Also, revisiting the topic of our patient's sister—she is being followed by a retinal specialist for AMD. While her vision is much worse than that of our patient's, it is unknown whether she too has MacTel. ■

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GCA: More than a Headache

If you suspect a diagnosis of giant cell arteritis, prompt referral for a work-up could help prevent a visual disaster. **By Joseph W. Sowka, OD, and Alan G. Kabat, OD**

The last Therapeutic Review column that discussed GCA was published in January 2007 (*see "Which Way to Treat GCA?"*). In it, we emphasized steroidal treatment for the condition, as well as possible alternate therapies.

Recently, however, we have been hearing far too many stories of vision loss associated with unrecognized or undiagnosed cases of GCA. While it is important to understand the proper medical therapy of GCA and its attendant complications, the most effective treatments are meaningless if the diagnosis is not made promptly and accurately.

Here are two brief case examples that underscore the fundamental importance of timely intervention:

Patient #1

A 78-year-old male who presented emergently with a blurry right eye and a two-month history of progressively worsening headache. He reported that over-the-counter analgesics provided no pain relief.

Before this visit, his internist ordered a CT scan and prescribed 800mg ibuprofen tablets TID, which minimally improved the headache. The CT scan returned normal.

Following the CT scan, the patient visited a chiropractor who diagnosed him with a tension headache secondary to a skeletal misalignment-induced muscle spasm. Unfortunately, multiple spinal adjustments yielded no symptom improvement. Additionally, the patient went to a dentist after he noticed that it hurt to chew his food. Even after the removal of a decayed tooth, his headaches persisted.

Best-corrected visual acuity in his right eye measured 20/80. Pupillary testing revealed a relative afferent defect OD. Ophthalmoscopically, he exhibited a slightly pale, mildly edematous optic disc with several parapapillary hemorrhages OD.

Based upon the clinical presentation and history, we tentatively diagnosed him with arteritic anterior ischemic optic neuropathy (AAION) in his right eye and immediately sent him to a hospital emergency room. A markedly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, along with subsequent temporal artery biopsy, confirmed that he had giant cell arteritis (GCA). Despite receiving high-dose intravenous steroids that same day, he progressed to total blindness in his right eye by the next morning. Remarkably, his left eye was unaffected.

Patient #2

A 74-year-old female who presented for a routine eye exam. She was bilaterally pseudophakic and correctable to 20/20 in each eye. At the end of the examination, she was slightly distraught to learn that her prescription didn't change; she mentioned experiencing headaches for several weeks and thought her glasses might have been to blame.

There was nothing abnormal in her examination, but a new-onset headache in a woman her age was concerning. Upon further questioning, she also admitted feeling slightly more fatigued than normal.

We sent the patient to her internist with a note to consider an evaluation for GCA. Her ESR and CRP readings were both mildly elevated. The internist then referred her to a rheumatologist who believed that the findings were consistent with GCA. So, she was started on a regimen of oral steroids, which quickly resolved her headaches. A temporal artery biopsy confirmed the diagnosis of GCA. Fortunately, however, she never lost vision.

Learn to Spot GCA

Patients suffering from giant cell arteritis typically are elderly, with a mean age of 71 at time of presentation. The prevalence of GCA increases with advanced age, and the condition usually isn't even considered in patients younger than age 50.[1] Women are somewhat more likely to develop GCA than men, and it is much more common in whites than blacks.[2]

A multitude of systemic manifestations can signal the presence of GCA. These include malaise, weight loss and anorexia, headache (typically in the temporal or occipital region), pulseless and indurated temporal arteries, night sweats, tongue necrosis and oral ulceration, dental abscess, scalp pain, scalp necrosis, jaw claudication when eating, head and neck swelling, anemia, depression, mental disturbance, neck pain, low-grade fever, transient ischemic

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attack and stroke, proximal myalgia, breast masses, gynecological disorders, malignant disease, persistent flu-like illness, chronic pharyngitis, vertigo, muscle aches, cardiac arrhythmia, congestive heart failure and myocardial infarction.[3-11]

GCA is a granulomatous inflammation of medium- and large-sized arteries that have a defined internal and external elastic lamina.[3] T lymphocytes, macrophages, histiocytes, plasma cells and multinucleate giant cells infiltrate the muscular wall of these vessels.[12,13] The resultant inflammation fragments the vascular walls, and leads to vessel lumen collapse and secondary ischemia.

Because virtually any vessel within the body may be involved, GCA is considered a multi-system, multi-symptom disorder. The degree of ischemia tolerated varies by system, and there often is a symptomatic period of weeks to months before the correct diagnosis is made. Prior to complete vascular occlusion and vision loss, this ischemia often manifests as cotton wool spots in the retina, transient ischemic attacks, amaurosis fugax, and intermittent diplopia and ophthalmoplegia.

All too often, patients with GCA are diagnosed following sudden, devastating vision loss in one or both eyes. The cause typically is AAION.[3,14,15]

The optic disc will be swollen, edematous, pale and atrophic, often with associated splinter hemorrhages. Typically, the associated disc edema is described as "chalky white."

GCA is the underlying cause in approximately 10% of central retinal artery occlusion (CRAO) cases, and must be suspected when encountering CRAO in elderly individuals.[15] Progression from unilateral to bilateral vision loss can occur within hours to days.

Work-up and Treatment

Once GCA is considered as a potential diagnosis, ESR and CRP must be ordered. If either level is elevated, or there are obvious constitutional symptoms, a temporal artery biopsy must be performed in order to conclusively diagnose GCA.

Systemic steroids are needed to preserve vision and reduce morbidity and mortality.[16-18] One report recommends that patients with vision loss or other ocular complications should receive three to four daily infusions of 250mg methylprednisolone for three days.[19]

For oral administration, the initial prednisolone dose is 60mg to 80mg per day. The dose should be reduced by 5mg to 10mg per week until the patient is taking 20mg per day; then a weekly decrease of 2.5mg until the patient is taking 10mg per day; and finally a dose reduction of 1mg per month until regimen completion. This schedule should be adjusted as needed, depending on the patient's symptoms and ESR or CRP.

Keep in mind that steroids should never be withheld while waiting for biopsy results. If the patient history, exam findings and serology are indicative of GCA, steroids must be started without delay. Biopsy results will not be immediately affected by the initiation of steroid therapy.

Elderly patients with ischemic neuropathy or artery occlusions and additional systemic symptoms need urgent management. Medical testing and systemic treatment must be done immediately. In most cases, this is best accomplished by sending the patient to a hospital emergency room with detailed notes on the ocular diagnosis and a recommendation for GCA evaluation.

Patients with GCA often present with no overt ocular findings at the time of diagnosis. However, headache in an elderly person is fairly atypical and extremely concerning. In these cases, referral to the patient's primary care provider for GCA evaluation is recommended. In fact, this is the best opportunity to avoid ensuing vision loss.

New-onset headache in the elderly can signal a host of things—from benign tension to a much more serious intracranial mass lesion or aneurysm. However, in cases of chronic, unremitting headache in older individuals, always consider GCA as a possible cause and act swiftly. ■

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Not Just Another 'Fish Story'

Dry eye suffers could benefit from supplements that contain fish oils and other fatty acids. **By Paul M. Karpecki, OD, and Diana L. Shechtman, OD**

Given the variability inherent within the dry eye population—it can affect just about anyone at any age, and its potential causes are numerous—obtaining statistically significant findings has been a challenge. Until now? At least in one aspect of care, perhaps. A nutritional supplement recently accomplished this feat in a randomized, double-masked, placebo-controlled multicenter trial led by John D. Sheppard, MD, MMSc, and Stephen C. Pflugfelder, MD. In the HydroEye Study, the researchers evaluated the effects of a dietary supplement on moderate-to-severe dry eye in postmenopausal women. The supplement consisted of black currant seed—a source of gama-linolenic acid (GLA)—and fish oils, a source of eicosapentaenoic acid and docosahexaenoic acid (EPA/DHA), antioxidants and nutrient co-factors.

Efficacy outcomes, assessed at baseline and at four, 12 and 24 weeks, included an Ocular Surface Disease Index (OSDI) questionnaire, Schirmer's test, tear break-up time, fluorescein and lissamine green staining, and corneal topographic indexes. Conjunctival impression cytologies were obtained and immuno-stained for inflammatory biomarkers. The results showed that the supplement treatment group had significantly improved dry eye symptoms. There was no progression of ocular surface inflammation, while inflammation worsened in the placebo group. Corneal irregularity, as measured by topographical indexes, was also maintained with supplement use, while surface irregularity progressed in the placebo group.

Understanding GLA

GLA is an omega-6 fatty acid (FA) found mostly in plant-based oils, such as borage seed oil, evening primrose oil and black currant seed oil. Omega-6 and omega-3 FAs are considered essential fatty acids (EFAs), which means they're necessary for human health; however, our bodies don't manufacture either of these fatty acids, so they must be ingested. A healthy diet contains a balance of omega-3 and omega-6 FAs.

Omega-3 fatty acids help reduce inflammation, whereas some omega-6 FAs promote it. Unfortunately, the typical American diet tends to favor the pro-inflammatory omega-6 variety, which is often found in animal fats and vegetable oils.

Notably, not all omega-6 fatty acids behave the same. Linoleic acid (LA) and arachidonic acid (AA) are typically considered less healthy because they promote inflammation. GLA, on the other hand, can reduce it, because much of the supplemental GLA is converted to an anti-inflammatory substance called dihomo-γ-linolenic acid (DGLA). But to help promote the conversion of GLA to DGLA, the body must be nourished with certain nutrients, including magnesium, zinc, and vitamins C, B3 and B6.

Fish Oil is Essential

Most ingested omega-6 fatty acids come from vegetable oils in the form of LA. The body converts LA to GLA and then to AA in a pro-inflammatory pathway. Without the presence of omega-3 fatty acids (ideally, from antioxidant-rich foods such as cold water fish or flaxseed), you can actually promote inflammation. You can achieve effective anti-inflammatory properties by maintaining a ratio of at least 1:1.

Clinical Research Concerning GLA + EPA/DHA

The clinical research related to ocular disease treatment and these EFAs is surprisingly abundant.

In 2011, researchers compared this combination to placebo and found statistical improvement in dry eye disease. Another study looked at the effects of a supplement involving LA, GLA and artificial tears on inflammatory markers in addition to typical dry eye testing. Interestingly, the results revealed statistically significant changes in symptoms ($p<0.005$), lissamine green staining ($p<0.005$) and ocular surface inflammation ($p<0.05$) in the study group, compared with controls as measured by human leucocyte antigen-DR (HLA-DR) expression reduction. There was no statistical improvement in TBUT or Schirmer's testing.

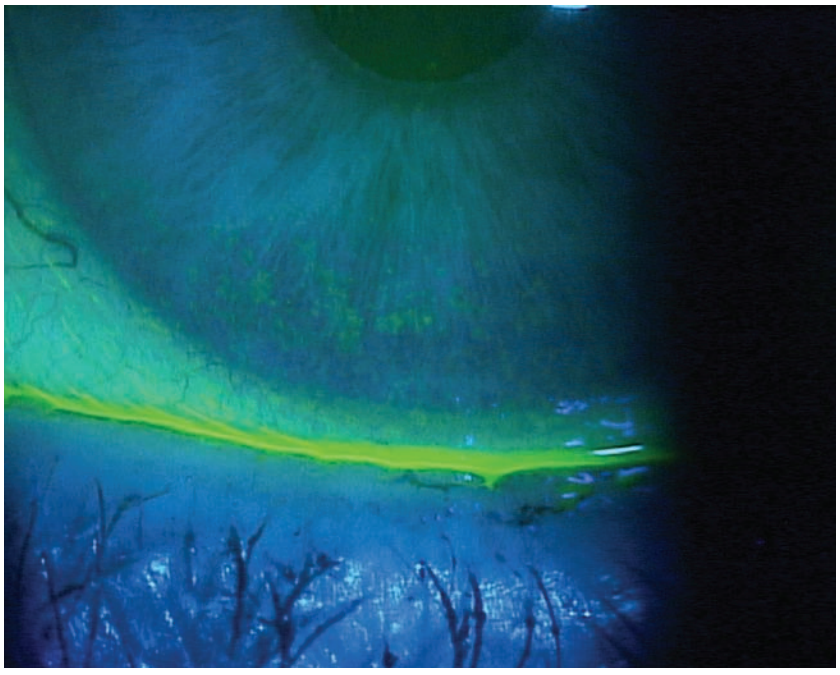
Research has also supported the benefits of GLA in the management of dry eye associated with contact lens use. In this study, the treatment group showed significant improvement in the specific symptom of "dryness" at three and six months ($p<0.01$) and also a significant

improvement in overall lens comfort at six months ($p<0.01$). Tear meniscus height was increased in the treatment group at six months relative to baseline ($p<0.01$), although all other objective signs were unchanged.

Patients with more advanced dry eye disease, such as Sjögren's syndrome KCS, also seemed to benefit. GLA supplementation was shown to improve symptoms and corneal staining signs. More specific studies into post-refractive surgery (PRK) dry eye also showed statistical improvement in symptoms and signs, such as tear production clearance.

Another study—once again, supporting the combination of GLA with EPA/DHA Omega-3 fatty acids—showed a statistical improvement in conjunctival inflammatory markers in dry eye patients after three months of use. The measurement for inflammation improvement was the reduction in conjunctival epithelium expression of the inflammatory marker HLA-DR. This study demonstrated that supplementation with omega-3 and omega-6 fatty acids can reduce expression of HLA-DR conjunctival inflammatory markers and may help improve DES symptoms.

Finally, there is also research supporting the benefits of GLA in meibomian gland dysfunction. In this study, patients were divided into three groups; the first received supplement containing GLA, the second lid hygiene and the third received both. Statistically significant improvement in symptoms occurred in all groups. After 180-day therapy, group one showed significant reduction in secretion turbidity ($p=0.02$) and meibomian gland obstruction ($p=0.0001$), whereas group two had significant reduction in eyelid edema ($p=0.02$), corneal staining ($p=0.01$), secretion turbidity ($p=0.01$) and meibomian gland obstruction ($p=0.0001$). Group three had significant reduction in eyelid edema ($p=0.003$), foam collection in the tear meniscus ($p=0.02$), corneal staining ($p=0.02$), secretion turbidity ($p=0.0001$) and meibomian gland obstruction ($p=0.0001$).



An incomplete blink in a patient with dry eye.

The importance of maintaining significant levels of omega-3 essential fatty acids in the body cannot be emphasized enough. The clinical benefit of GLA is well-supported as a proper supplement to promote DGLA formation and anti-inflammatory effects. GLA may well be a valuable component to ocular surface disease health, perhaps similar to what we've seen in macular disease research related to lutein, xeaxanthin and mesoxeaxanthin carotenoids. ■

Disclosures: Paul M. Karpecki has received compensation in the form of research grants, consulting fees, advisory board participation or speaker honoraria from the following companies: Akorn, Alcon, Allergan, AMO, Bausch + Lomb, MacuHealth, OcuSoft, PRN, Science Based Health and ZeaVision.

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Meetings + Conferences

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■ **23-27.** *American Academy of Optometry-New Jersey Chapter.* Kingston Plantation, Myrtle Beach, SC. Hosted by: New Jersey Chapter. Key faculty: Randall Thomas, OD, Ron Melton, OD, Marc Bloomenstein, OD. CE hours: 16. Email Dennis Lyons, OD, dhl2020@aol.com, or call (732) 920-0110.

■ **24-26.** *Mountain West Council of Optometrists Annual Congress.* Caesars Palace, Las Vegas. Hosted by: MWCO. CE hours: 24. Call 1-888-376-6926. Visit www.mwco.org.

■ **24-26.** *59th Annual Education Meeting.* Hilton Savannah DeSoto, Savannah, Ga. Hosted by: Contact Lens Society of America. Key faculty: Patrick Caroline, FAAO, Craig Norman, FCLSA, Michael Ward, FCLSA, Jason Jedlicka, OD, Brooke Messer, OD, Edward Bennett, OD, Stephen Byrnes, OD. CE hours: 22. Email Tina Schott at tinaschott@clsa.info or call (703) 437-5100. Visit www.clsa.info.

■ **24-27.** *KOA 2014 Spring Congress.* Hyatt Hotel & Lexington Convention Center, Lexington, Ky. Hosted by: Kentucky Optometric Association. CE hours: 21. Email Sarah Unger at sarah@kyeyes.org or call (502) 875-3516. Visit www.kyeyes.org.

■ **24-27.** *Arkansas Optometric Association Spring Convention.* The Peabody, Little Rock, Ark. Hosted by: Arkansas Optometric Association. Email aroa@arkansasoptometric.org. Visit www.arkansasoptometric.org.

■ **25-27.** *2014 Annual CE Symposium.* Renaissance O'Hare, Chicago, Ill. Hosted by: The Optometric Society and Optometric CE. Key faculty: James Fanelli, OD, Ernie Bowling, OD, Robert Rebello, Steven Newman, OD. CE hours: 14. Email Joel Rothschild at admin@optometricce.org. Visit www.optometricce.org.

■ **26-27.** *22nd Annual Suncoast Seminar.* Hyatt Regency Clearwater Beach Resort and Spa, Clearwater, Fla. Hosted by: Pinellas Optometric Association. CE hours: 14. Email idoc1@aol.com or call (727) 446-8186. Visit www.optometricce.org.

May 2014

■ **2.** *Berkeley Glaucoma Day - 2nd Annual.* DoubleTree Hotel, Berkeley Marina, Berkeley, Calif. Hosted by: University of California, Berkeley, School of Optometry. Email optoCE@berkeley.edu. Visit awww.aoa.org/events/ucb-glaucoma-day.

■ **2-3.** *Educational Meeting 2014.* Mission Inn, Howey-in-the-Hills, Fla. Hosted by: Florida Chapter of the American Academy of Optometry. Featured speakers: Leo Semes, OD, Albert Woods, OD, and Tim Underhill, OD. CE hours: 10. Contact Arthur T. Young, OD, at eyeguy4123@msn.com.

■ **2-4.** *CE in Italy.* Rome, Italy. Hosted by: James Fanelli, OD. Key faculty: Joe Pizzimenti, OD, Carlo Pelino, OD, James Fanelli, OD. CE hours: 12. Contact James Fanelli, OD, at jamesfanelli@CEinItaly.com or call (910) 452-7225.

■ **2-4.** *May Annual Eye Care Conference & Alumni Reunion.* Nova Southeastern University, Ft. Lauderdale, Fla. Hosted by: Nova Southeastern University. Key faculty: Carlo Pelino, OD. CE hours: 18. Contact Vanessa McDonald at oceaa@nova.edu or call (954) 262-4224.

■ **4-8.** *ARVO Annual Meeting.* Orange County Convention Center, Orlando, Fla. Hosted by: ARVO. Email arvo@arvo.org.

■ **7-8.** *118th Annual Meeting and Spring Seminar.* DeVos Place, Grand Rapids, Mich. Hosted by: Michigan Optometric Association. CE hours: 12. Contact Amy Root at amy@themoa.org or call (517) 482-0616.

■ **10-19.** *AEA Cruises Mediterranean Cruise Seminar.* Athens to Venice. Hosted by: AEA Cruises. Key faculty: Louise Sclafani, OD, Mark Roanova, OD. CE hours: 12. Contact Marge McGrath at aeacruises@aol.com or call (888) 638-6009.

■ **29-31.** *Oregon's Meeting.* Bend Riverhouse Hotel and Conference Center, Bend, Ore. Hosted by: Oregon Optometric Physicians Association. Key faculty: Jane Weissman, MD, Thomas Hwang, MD, Greg Kaultz, OD, Ryan Bulson, OD, Mark Andre, FAAO. CE hours: 11. Contact Lynne Olson at lynne@oregonoptometry.org or call (800) 922-2045.

■ **30-June 1.** *Ocular Symposium: Pearls in Ocular Diagnosis.* San Francisco, Calif. CE hours: 24. Contact Lorraine Geary at ocularsymp@aol.com or call (415) 278-9940.

June 2014

■ **8.** *Resident Forum.* UC Berkeley Campus, Berkeley, Calif. Hosted by: University of California, Berkeley, School of Optometry. CE hours: 8. Email mmoy@berkeley.edu or call (510) 642-8802. Visit optometry.berkeley.edu/ce/introduction.

■ **13-14.** *Northwest Residents Conference.* Jefferson Hall on Pacific University Campus, Forest Grove, Ore. Hosted by: Pacific University College of Optometry. CE hours: 10. Email Martina Fredericks at frederim@pacificu.edu or call (503) 352-2207. Visit www.pacificu.edu.

■ **20-22.** *100th Anniversary Annual Convention.* Crowne Plaza Hotel, Baton Rouge, La. Hosted by: Optometry Association of Louisiana. Featured speakers: Larry Alexander, OD, James Thimons, OD, Randall Thomas, OD, Ron Melton, OD. CE hours: 16. Email optla@bellsouth.net or call (318) 335-0675. Visit www.optla.org.

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■ **25-28.** *2014 Optometry's Meeting.* Pennsylvania Convention Center, Philadelphia. Hosted by: AOA. CE hours: 180. Email office@thevoa.org or call (804) 643-0309. Visit www.thevoa.org.

■ **29-July 14.** *AEA Cruises.* Grand Princess, Alaska. Hosted by: AEA Cruises. CE hours: 10. Email aeacruises@aol.com or call (888) 638-6009. Visit www.optometriccruiseseminars.com.

July 2014

■ **10-13.** *Colorado Vision Summit.* Steamboat Grand Hotel,

Steamboat Springs, Colo. Hosted by: Colorado Optometric Association and Mountain States Congress of Optometry. Featured speakers: Andrew Gurwood, OD, Marc Myers, OD, Marc Bloomenstein, OD, Leo Semes, OD, Cathy Stern, OD, WC Maples, OD, Kyle Cheatham, OD, Mile Brujic, OD, Steve Devick, OD. CE hours: 52. Email CVSummit@visioncare.org or call (877) 691-2095. Visit www.coloradovisionsummit.org.

■ **10-19.** *Therapeutic Pharmaceutical Agents Certification Course.* Nova Southeastern University, Fort Lauderdale, Fla. Hosted by: Nova Southeastern University. Featured speakers: Bruce Onofrey, OD, Kim Reed, OD, Joseph Sowka, OD. CE hours: 100. Email oceaa@nova.edu or call (954) 262-4224. Visit optometry.nova.edu/ce/index.html.

■ **24-27.** *Florida Optometric Association's Annual Convention.* Boca Raton Resort & Club, Boca Raton, Fla. Hosted by: Florida Optometric Association. CE hours: 22. Email Blake Moore, blake@floridaeyes.org or call (850) 877-4697. Visit www.floridaeyes.org.

■ **25-27.** *Tahoe Summit.* Hyatt Regency, Incline Village, Nev. Hosted by: Sacramento Valley Optometric Society. CE hours: 12. Email Jerry Sue Hooper at jerrysue13@comcast.net or call (916) 446-2331.

■ **26-28.** *National Glaucoma Symposium.* Ocean Edge Resort, Brewster (Cape Cod), Mass. Hosted by: National Glaucoma Society. CE hours: 18. Email Blake Moore at info@NationalGlaucomaSociety.org or call (877) 825-2020. Visit www.NationalGlaucomaSociety.org.

August 2014

■ **1-3.** *South Seas Educational Retreat.* South Seas Island Resort, Captiva Island, Fla. Hosted by: Southwest Florida Optometric Association. Featured speakers: Ben Gaddie, OD, Carlo Pelino, OD, April Jasper, OD, Ron Foreman, OD. CE hours: 18. Email swfoa@att.net or call (239) 481-7799. Visit www.swfoa.com.

■ **1-3.** *Smoky Mountain Summer.* Grove Park Inn, Asheville, NC. Hosted by: Nova Southeastern University. Featured speakers: Diana Shechtman, OD, Bill Jones, OD. CE hours: 14. Email oceaa@nova.edu or call (954) 262-4224. Visit optometry.nova.edu/ce/index.html.

September 2014

■ **13-14.** *Diabetic Management Update and Annual Glaucoma Meeting.* Nova Southeastern University, Ft. Lauderdale, Fla. CE hours: 12. Email oceaa@nova.edu or call (954) 262-4224. Visit optometry.nova.edu/ce/index.html.

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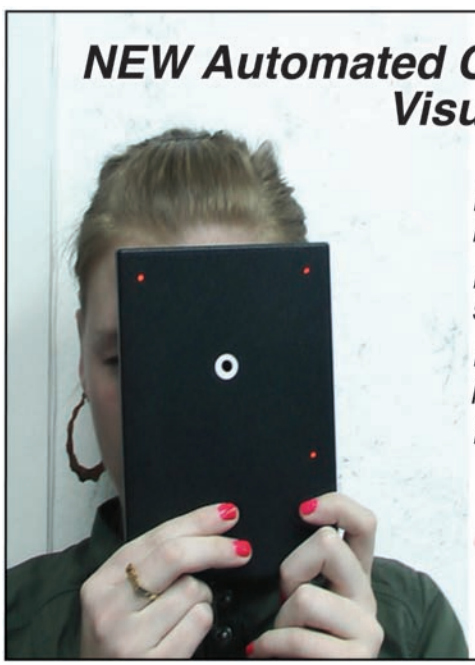

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Edited by Derek N. Cunningham, OD, and Walter O. Whitley, OD, MBA

Band on the Run

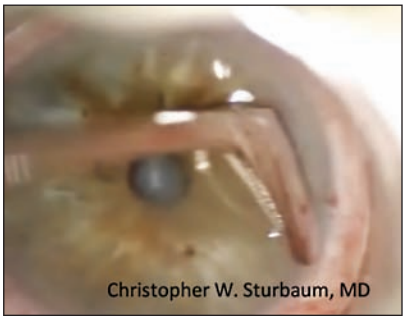
Chelation via EDTA, effective in clearing band keratopathy, may be warranted earlier in the disease course. By Casey D. Claypool, OD, and Christopher W. Sturbaum, MD

Band keratopathy, a relatively common corneal dystrophy caused by calcification of the anterior stroma and Bowman's layer, usually occurs between the palpebral fissures, starting peripherally and then progressing to the center. The cornea has rough, white, plaque-like patches separated from the limbus by clear cornea. There may be "holes" in the calcium deposits, which can give it a Swiss cheese appearance.[1]

Symptomatology can vary widely, from asymptomatic patient histories to those who describe decreased vision and severe foreign body sensation (directly proportional to the density of the deposits). There are several possible etiologies; the most common include idiopathic causes, dry eye, chronic uveitis, glaucoma, corneal edema and hypercalcemia. Additionally, conditions to consider in the differential include gout, interstitial keratitis, primary and secondary calcareous corneal degeneration, calciphylaxis and spheroidal degeneration. Also, consider the potential for an ocular and systemic hypersensitivity reaction characterized by calcium deposition in response to specific antigens or agents.

Collaboration is Key

Communication with the PCP is essential in managing these patients, as a work-up for hyperparathyroid, sarcoid, gout or renal failure may be needed.[2,3] Prolonged exposure to chemicals such as mercury and intraocular substances (e.g., silicone oil) can also cause band keratopathy. These are important to remember—pilocarpine contains mercurial preservatives, for instance, and silicone oil is commonly used in retinal detachment surgery. Thus, it is essential to monitor for corneal changes over time.[4]



Go to www.revoptom.com or scan the QR code at left to see video of a chelation procedure.

If the patient only experiences mild foreign body sensation with no effect on vision, treating with topical lubrication—as you would treat ocular surface disease—may suffice. As the patient progresses to visual acuity loss, increased foreign body sensation or increased cosmetic concerns, further intervention is warranted. The recommended course is chelation by disodium ethylenediaminetetraacetic acid (EDTA).

In the chelation procedure, the cornea is prepped by gentle epithelial debridement with a spud or scalpel, then a corneal well is placed on the eye and disodium EDTA 3% is added to it. As seen in the accompanying video, the solution alone will dissolve the calcium precipitates, but gentle rubbing of the plaques increases the break-up time. Once completed, the EDTA is rinsed off the cornea and a bandage contact lens is inserted for comfort until the cornea is re-epithelialized.[3]

Post-op medications include topical antibiotics, NSAIDs and steroids for comfort and treatment of inflammation and corneal edema. These can be stopped once the epithelium is healed and the bandage lens is removed. Additional treatment options include phototherapeutic keratectomy or superficial debridement, which generally restore vision and comfort for most patients with band keratopathy.

In our practice, we had traditionally waited until patient symptoms were severe before EDTA treatment was recommended. Now, we have found that early intervention improves patient comfort and vision, and prevents further stromal scarring. Due to the minimally invasive nature of the treatment, early intervention is often very much appreciated by the patient.

It is important to remember that the recurrence rate of band keratopathy is high. However, the chances can be reduced if the underlying cause is addressed promptly upon diagnosis. ■

Drs. Claypool and Sturnbaum practice together at Empire Eye in Spokane, Wash.

1. Jhanji V, Rapuano CJ, Vajpayee RB. Corneal calcific band keratopathy. Curr Opin Ophthalmol. Jul 2011;22(4):283-9.
2. Porter R, Crombie AL. Corneal and conjunctival calcification in chronic renal failure. Br J Ophthalmol. May 1973;57(5):339-43.
3. Ehlers J, Shah C. Band Keratopathy. Wills Eye Manual. 2008; 60-62.
4. Available at: http://dro.hs.columbia.edu/bandk.htm.

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Diagnostic **Quiz**

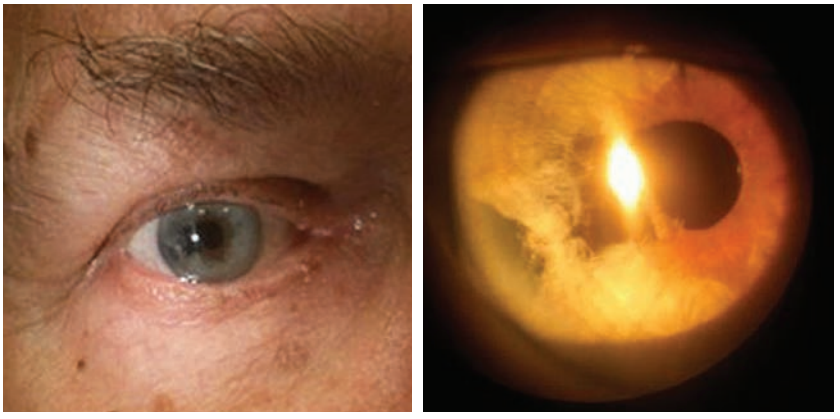
The Ol' Flomax Flop

By Andrew S. Gurwood, OD

History

An 82-year-old white male presented with a chief complaint of photophobia and glare in both eyes. His ocular history was remarkable for bilateral cataract surgery nine months earlier.

His systemic history was significant for a heart triple bypass and prostate cancer. Additionally, he reported using Flomax (tamsulosin, Boehringer Ingelheim) for several years before his cataract procedure. The patient had no known allergies of any kind.



The right eye of our 82-year-old patient who presented with a history of cataract surgery and Flomax use. What is the correct diagnosis?

Diagnostic Data

His best-corrected visual acuity measured 20/25 OD and 20/20 OS. His pupillary evaluation revealed no evidence of afferent defect. Extraocular muscle movements were full and unrestricted.

There was no evidence of corneal pathology or anterior chamber reaction OU. Intraocular pressure measured 18mm Hg OU. The dilated fundus examination revealed normal and quiet grounds in both eyes.

The pertinent clinical findings OD are illustrated in the photographs.

Your Diagnosis

How would you approach this case? Does the patient require any additional tests? What is the most likely diagnosis?

How would you most effectively manage this patient? What is the prognosis?

To find out, please visit www.revoptom.com. Click on the cover icon for this month's issue, and then click "Diagnostic Quiz" under the table of contents. ■

Retina Quiz Answers *(from page 89):* 1) d; 2) c; 3) b; 4) a; 5) a.

Next Month in the Mag

May features our 19th Annual Comanagement Report. Topics include:

- *Omni Eye Centers: Success Stories in Optometric Comanagement*
- *Glaucoma Comanagement in the MIGS Era: Your Essential Role*
- *Gear Up for Neuro-ophthalmic Comanagement*

Also inside:

- *Optometric Study Center: Practical Protocols for Herpes Simplex Keratitis* (earn 2 CE credits)

Feedback

Review of Optometry welcomes questions and comments. E-mail Jack Persico, editor-in-chief, jpersico@jobson.com, with "Letter to the Editor" as the subject line.

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ILEVRO™

(nepafenac ophthalmic suspension) 0.3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO™ Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO™ Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO™ Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO™ Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO™ Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO™ Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension, 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.

Corneal Effects
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 ILEVRO™ Suspension and should be closely monitored for corneal health. Postmarketing 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.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO™ Suspension should not be administered while using contact lenses.

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

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased post-implantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO™ Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO™ Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO™ Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO™ Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO™ Suspension in pediatric patients below the age of 10 years have not been established.

Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Contact Lens Wear
ILEVRO™ Suspension should not be administered while wearing contact lenses.

Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Shake Well Before Use
Patients should be instructed to shake well before each use. U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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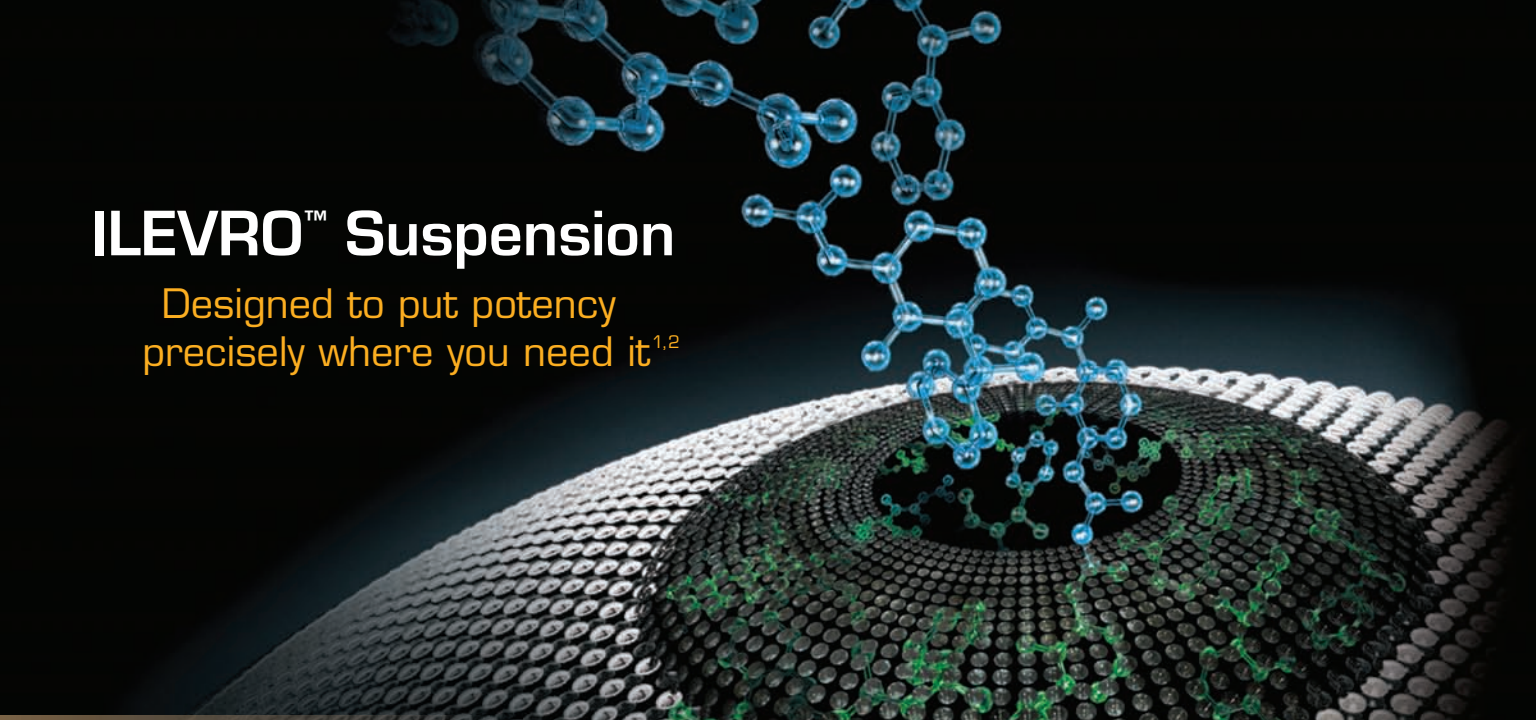

ILEVRO™ Suspension

Designed to put potency precisely where you need it[1,2]

ONCE-DAILY POST-OP

One drop should be applied once daily beginning 1 day prior to surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery[3]

Use of ILEVRO™ Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events[3]

INDICATIONS AND USAGE

ILEVRO™ Suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration

One drop of ILEVRO™ Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO™ Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- Increased Bleeding Time – With some nonsteroidal anti-inflammatory drugs including ILEVRO™ Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some 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.

  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.

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- Contact Lens Wear – ILEVRO™ Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO™ Suspension, please refer to the brief summary of prescribing information on adjacent page.

References: 1. Ke T-L, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation, II: In vitro bioactivation and permeation of external ocular barriers. *Inflammation.* 2000;24(4):371-384. **2.** Data on file. **3.** ILEVRO™ Suspension package insert.

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