

REVIEW *of* OPTOMETRY

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—EARN 2 CE CREDITS

HOW SYSTEMIC DRUGS TRIGGER DRY EYE

Learn how to spot—and rectify—these
adverse effects. p. 66

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OCULAR SURFACE DISEASE REPORT:

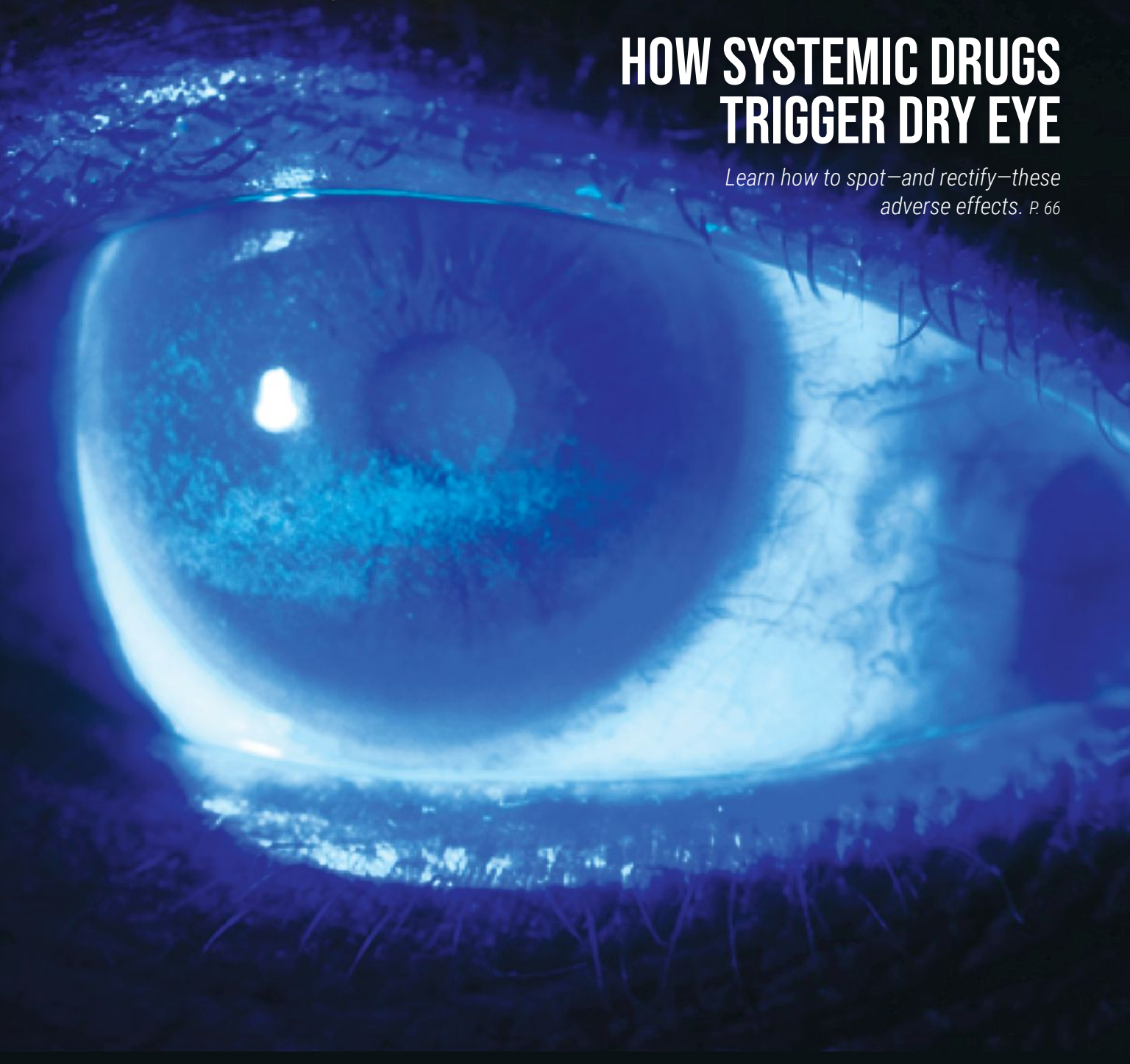
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VYZULTA
(latanoprostene
bunod ophthalmic
solution), 0.024%

THE HORSEPOWER YOU NEED TO LOWER IOP

Powerful IOP reduction with excellent tolerability^{1,2}

VYZULTA delivered **up to 9.1 mmHg mean IOP reduction** from baseline in pivotal trials.^{1,2*}

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*Pivotal study designs: Two Phase 3, randomized, multicenter, parallel-group studies, APOLLO and LUNAR, evaluating noninferiority of once-daily VYZULTA vs twice-daily timolol maleate 0.5% in patients with open-angle glaucoma or ocular hypertension. Primary endpoint was IOP measured at 9 assessment time points in study eye. APOLLO (VYZULTA, n=284; timolol, n=133) and LUNAR (VYZULTA, n=278; timolol, n=136).^{2,3}

INDICATION

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence $\geq 2\%$ are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

For more information, please see Brief Summary of full Prescribing Information on adjacent page.

References: **1.** VYZULTA Prescribing Information. Bausch & Lomb Incorporated. **2.** Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973. **3.** Medeiros FA, Martin KR, Peace J, Scassellati Sforzolini B, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA® (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly [see Patient Counseling Information (17) in full Prescribing Information].

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

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 practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 $\mu\text{g}/\text{kg}/\text{day}$ (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension

and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 $\text{mcg}/\text{kg}/\text{day}$ (87 times the clinical dose) [see Data].

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 $\text{mcg}/\text{kg}/\text{day}$. Abortion occurred at doses ≥ 0.24 $\text{mcg}/\text{kg}/\text{day}$ latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 $\text{mcg}/\text{kg}/\text{day}$ and late resorptions at doses ≥ 6 $\text{mcg}/\text{kg}/\text{day}$ (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 $\text{mcg}/\text{kg}/\text{day}$ (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 $\text{mcg}/\text{kg}/\text{day}$ (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 $\text{mcg}/\text{kg}/\text{day}$. Maternal toxicity was produced at 1500 $\text{mcg}/\text{kg}/\text{day}$ (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 $\text{mcg}/\text{kg}/\text{day}$ (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 $\text{mcg}/\text{kg}/\text{day}$ (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

U.S. Patent Numbers: 7,273,946; 7,629,345; 7,910,767; 8,058,467.

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VA Expands Scope of Practice for its ODs

Guidelines that previously stated that “only” ophthalmologists can perform invasive procedures have been revised to include “or optometrists,” provided the state law allows it.

Optometrists employed by the US Department of Veterans Affairs must comply with the organization’s national standard of practice guidelines, which previously denied ODs the ability to perform invasive ocular procedures, even if permissible in their state of licensure. However, thanks to a recent update to the language in these guidelines, VA optometrists—rather than exclusively ophthalmologists—are allowed to perform various advanced ocular procedures, including laser and other types of eye surgery, injections and lesion removal based on the scope of practice of each provider’s state of licensure.

The change follows persistent advocacy from the American Optometric Association (AOA), Armed Forces Optometric Society (AFOS), Mississippi Optometric Association (MOA) and members of Congress, after one recent circumstance brought attention to the need for VA guidelines to be modified to reflect the current scope of practice.

“In March 2022, a Mississippi doctor of optometry providing routine care to a veteran in the community was denied coverage by the local VA system to diagnose and treat trichiasis with entropion due to the former language in the Eye Comprehensive Standardized Episode of Care,” noted an AOA story the about the win.¹ “The VA reportedly suggested that the doctor refer the veteran to an ophthalmologist nearly 60 miles away for needed epilation.”

In response to concerns from vets, lawmakers and organizations such as the MOA, AOA and AFOS, the VA changed the language of these guidelines to state “an ophthalmologist *or* optometrist can perform invasive procedures, including injections, lasers and eye surgery.”



The policy change brings ODs in the VA system to parity with the rest of their in-state colleagues.

In 2021, Mississippi lawmakers expanded the state’s scope of practice for ODs to include injections, excision and removal of benign lid lesions and chalazia, YAG capsulotomy and greater prescribing authority. Several other states have added advanced procedures to their optometric scope of practice in recent years, including Alaska (2017), Arkansas (2019), Wyoming (2021) and, just this year, Virginia and Colorado. Now, VA optometrists in any of these states can take advantage of the new practice rights and offer a higher level of care to veterans, which Kris May, OD, legislative chair of the Mississippi Optometric Association, notes is most important.

“Many states have expanded their scope of practice for optometrists, recognizing their training and abilities can provide expanded access and excellent care for their residents,” says Dr. May. “It is encouraging to see the Veterans Administration do the same. My hope is that this model carries forward into the VA’s national standard of practice guidelines so our veterans continue to have access to the care they deserve.”

Stacie Moore, OD, MOA president, adds that because of the change, “vet-

erans now have an expanded list of licensed ODs allowing for time-efficient, quality eye care.” She also says, “the language change builds momentum for a national expanded scope of practice for VA optometrists.” Marc Myers, OD, who’s worked with the VA for over 15 years, agrees that “the primary benefactor, both locally and nationally, is veterans who benefit from improved access to quality eye care.”

A recent article on American Academy of Ophthalmology’s website pushing back on the VA’s decision states that “several leading medical schools are concerned that [the] recent change will put veterans’ eye care in significant jeopardy.” The article cites differences in surgical training standards for optometrists vs. ophthalmologists as the primary reason for opposing the change.

The VA has been working towards establishing a national standard of practice that would allow any licensed OD within the VA system to perform procedures the agency designates, superseding individual state scope regulations. The Federal Supremacy Project, as it’s called, will set scope parameters for at least 50 different healthcare professions that provide care within the VA network. Optometry’s standards are expected to be released within the first few months of 2023, with a decision expected closer to the end of next year. ◀

1. Veterans notch win as VA rescinds restrictive language governing community ODs. American Optometric Association. Published November 3, 2022. www.aoa.org/news/advocacy/federal-advocacy/veterans-notch-win-as-va-rescinds-restrictive-language-governing-community-ods. Accessed November 7, 2022.

2. Academic center chairs speak up to protect quality veteran eye care. American Academy of Ophthalmol. Published October 27, 2022. www.aao.org/eye-on-advocacy-article/chairs-speak-up-protect-quality-veterans-eye-care. Accessed November 7, 2022.

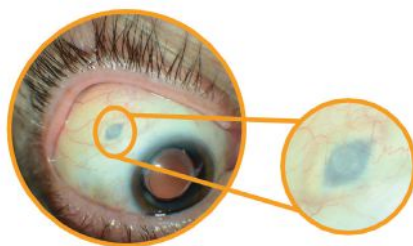
Susvimo AMD Implant Recalled Due to Potential for Leakage

Once production issues are resolved, the product is expected to re-enter the market.

Around this time last fall, the FDA approved the first sustained-release drug delivery system for wet AMD, the intravitreal implant Susvimo (100mg/mL ranibizumab injection, Genentech/Roche), a novel treatment approach requiring a medication refill only every six months. Fast forward to this year and the product is being pulled from US shelves due to a voluntary manufacturer recall relating to a potential leakage problem.

Between twice-yearly treatments, the implant is designed to dispense the anti-VEGF agent into the vitreous in a controlled manner. However, in late October Roche CEO Bill Anderson explained in an investor call that, due to a manufacturing issue, the company

has cause for concern that there may be a problem with the seal on the intravitreal device that's intended to prevent the medication from leaking out after it's injected. As reported in the industry publication *Fierce Pharma*, Mr. Anderson communicated Roche's concern about the possibility that the seal could fail after repeat dosing and



Patients with the implant do not require explantation and will continue to receive drug refills as needed, Roche explained.

is quoted as saying, "because it didn't meet our performance standards, and [because] we want to make sure that we have high reliability, we decided to voluntarily stop distribution of the port delivery system."¹

Roche advises patients who already have the Susvimo implant to continue receiving refills as normal, and notes that explantation is not necessary. However, no new patients will be able to receive the implant until the production issues are resolved and the device returns to the market, which the company estimates will be approximately within a year or so. ◀

Kansteiner F. Roche recalls new eye therapy Susvimo on leakage fears, aims for market return 'within a year or so'. Fierce Pharma. Published October 18, 2022. www.fiercepharma.com/manufacturing/roche-recalls-susvimo-implant-lucentis-leakage-fears-return-market-expected-within. Accessed October 19, 2022.

Photo: Anat Loewenstein, MD

Rare But Possible: Vision Loss Due to COVID-19

The leading cause was optic neuropathy, recent study suggests.

While impairments in taste and smell are commonly known COVID effects, reduced visual acuity (VA) has been reported far less often. A recent systematic review and meta-analysis aimed to identify and describe the characteristics of the visual loss associated with COVID.

The study included articles reporting on vision loss development linked to COVID-19 infection. Visual loss was defined according to the International

Classification of Diseases as distance mild visual impairment: VA <0.5 but ≥0.3 using a decimal scale, distance moderate visual impairment: VA <0.3 but ≥0.1, distance severe visual impairment: VA <0.1 but ≥0.05, blindness: VA <0.05 and near visual impairment: VA <N6 at 40cm with existing correction.

After screening, the researchers selected 29 studies for inclusion: two cross-sectional studies, 24 case reports and three case series. A meta-analysis revealed a pooled visual loss cumulative incidence in COVID-19 patients of 0.16.

The team's review found that the leading cause of visual loss across the studies was optic neuropathy. SARS-CoV-2 can affect the nervous system through different routes; it can enter this system through the bloodstream by infecting the choroid plexus or meninges or spreading through the olfactory nerves. A mechanism of molecular mimicry, in which viral antigens induce

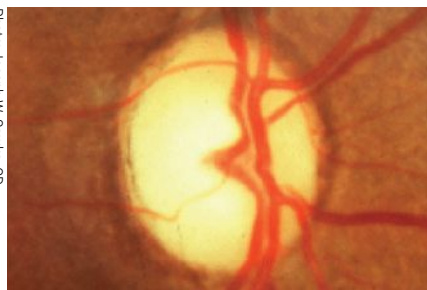
an immune response against self-proteins, may also be responsible for tissue injury.

The researchers also proposed that COVID-19 may lead to various opportunistic infections. The altered immune response and the use of corticosteroids may increase the risk of superadded infections after a prolonged period in intensive care units. During COVID-19, cytokines such as IL-6, IL-10 and TNF-α are markedly higher, whereas T lymphocytes are much lower.

"COVID-19 might cause visual loss through several mechanisms," the researchers wrote in their paper. "Therefore, it should be considered in patients who have recently developed visual loss, and clinicians should be aware of this uncommon event to avoid blindness in everyday clinical practice." ◀

Ripa M, Motta L, Shipa C, et al. "Vision loss" and COVID-19 infection: a systematic review and meta-analysis. *Vision*. 2022;5(4):60.

Photo: Joseph W. Sowka, OD



Assess all patients who have visual impairment symptoms during COVID-19.

A close-up photograph of a person's eye. The eye is partially closed, and the text "There's MORE Than meets The Eyelid" is written in black marker on the upper eyelid. The person has light brown hair and skin. The text is written in a casual, hand-drawn style.

There's **MORE**
Than meets
The Eyelid

CHRISTIAN, real DB patient
and ophthalmologist

We're willing to bet
most eye care professionals
don't realize just how prevalent
Demodex blepharitis is.¹

In fact, ~**25 million eye care patients** are
affected by *Demodex* blepharitis (DB).^{2,3}

DON'T BELIEVE US?
LEARN HOW EASILY DB CAN FLY UNDER THE RADAR AT

LOOK *at the* LIDS.COM



@LookAtTheLids



References: 1. Data on file, Tarsus Pharmaceuticals, Inc. June 2022. 2. Trattler W, Karpecki P, Rapoport Y, et al. The prevalence of *Demodex* blepharitis in US eye care clinic patients as determined by collarettes: a pathognomonic sign. *Clin Ophthalmol.* 2022;16:1153-1164. 3. Saydah SH, Gerzoff RB, Saaddine JB, Zhang X, Cotch MF. Eye care among US adults at high risk for vision loss in the United States in 2002 and 2017. *JAMA Ophthalmol.* 2020;138(5):479-489.

Most OMD Researchers Don't Disclose Conflicts of Interest

A study found that, in medical journals, nearly two-thirds reported none and only 1% reported all.

Transparency in clinical trials is vital to ensure the accuracy and neutrality of the studies and their results. Medical researchers who publish their work in a journal are required to disclose financial relationships involving companies they mention in the article; however, a recent study found that, in ophthalmology journals, the majority of clinical researchers fail to self-report their conflicts of interest.

The study group evaluated articles from several prestigious publications, including *Ophthalmology*, *JAMA Ophthalmology*, *American Journal of Ophthalmology* and *Investigative Ophthalmology & Visual Science*. Self-reported relationships were defined as the companies listed in the article's conflict of interest disclosures. That data was then compared with Open Payments Database (OPD)-reported relationships, defined as the list of companies that reported payments to the author within 36 months before submission. The term "authorship" was used to assess cases when an author published multiple articles.

Of the 660 total authorships (486 unique authors), a sizable 63% reported none of their OPD-reported relationships, 17% reported some and only 1% reported all. The remaining 19% had no conflicts of interest to disclose.

Authors who received more money during the reporting period were more likely to self-report financial relationships,

consistent with previous study findings. Author position and self-reporting had no association.

Although the researchers hypothesized that self-reporting would be higher in journals with more stringent policies for disclosing conflicts of interest, they found that this wasn't necessarily the case. "The proportion of authorships who self-reported none of their relationships was not significantly different between journals that require reporting of all relationships compared with journals that only require reporting of relevant relationships (adjusted percentage: 61.4% vs. 64.3%)," they wrote in their paper on the study.

The researchers proposed several reasons why authors may fail to report a financial relationship, one being that they might consider the relationship to be irrelevant to their research. "Some journals instruct authors to disclose only 'relevant' relationships, imposing a subjective decision on the author to determine when relevancy is strong enough to warrant reporting," the researchers wrote. "Authors may also omit reporting a relationship if they find it insignificant in terms of type or value." Another explanation is that authors could be unaware of payments listed in the OPD.

To ensure we can accurately interpret clinical studies, the researchers argued that steps must be taken to help increase self-reporting of conflicts of interest. In addition to a consistent

guideline for disclosure among journals, they suggested the idea that publications could move away from self-reporting altogether and rely solely on the OPD. "Industry reporting may be more reliable than author self-reporting, as reflected by the high number of relationships reported in the OPD that are omitted by authors," they wrote.

The researchers concluded, "Incomplete self-reporting in ophthalmology research gives the impression of lack of transparency and undermines confidence in the objectivity of ophthalmology research findings. Investigators registered in the OPD would be well-advised to be aware of the content of their OPD entries and to consider this content when self-reporting financial relationships in research manuscripts." ◀

Hwang ES, Liu L, Ong MY, et al. Self-reporting of conflicts of interest by ophthalmology researchers compared to the Open Payments Database industry reports. *Ophthalmology*. November 1, 2022. [Epub ahead of print].



Photo: Getty Images

Journal guidelines and author position weren't associated with self-reporting of financial interests; however, dollars received had a significant effect.

IN BRIEF

■ **Antihypertensive Drugs Unlikely to Affect Glaucoma Risk.** A recent study investigated the genetic correlation and causal association of IOP, systolic BP, diastolic BP and 12 antihypertensive drug classes with glaucoma. It found that **controlling BP may not help prevent and treat glaucoma, and antihypertensive drugs may not improve or worsen glaucoma.**

The study included data from the UK Biobank for glaucoma (patients: 4,737, controls: 458,196) and BP ($n=422,771$) and 12 European ancestry cohorts from the International Glaucoma Genetic Consortium for IOP ($n=31,269$).

Linkage disequilibrium score results showed a suggestive association of glaucoma with systemic BP ($R_g=0.12$) and diastolic BP ($R_g=0.17$). Univariate Mendelian randomization did not indicate that ge-

netically elevated BP in participants leads to an increased glaucoma risk (systemic BP odds ratio [OR]: 1.05, diastolic BP OR: 1.07). Univariate mendelian randomization was replicated in a multivariable setting (systemic BP OR: 0.95, diastolic BP OR: 1.13). Furthermore, the researchers found **insufficient evidence to suggest that antihypertensive drugs were associated with glaucoma.**

Assessing the role of BP on glaucoma from the genetic perspec-

tive may explain only part of the association.

The team concluded that their data **"provides valuable public health and clinical advice that the use of BP-lowering and antihypertensive drugs as interventions in patients with glaucoma remains open to question."**

Liu J, Li S, Hu Y, Qiu S. Repurposing antihypertensive drugs for the prevention of glaucoma: a mendelian randomization study. *Transl Vis Sci Technol*. 2022;11(10):32.

Early Advocacy

Why Young ODs Should Prioritize Advocacy for Optometry



Collin Gray, OD
Eyecare of Lehi
Lehi, Utah

Change happens because of action—or inaction. The future of optometry is in the hands of those dedicated to advocating for positive change for the benefit of patients, practices, and the profession as a whole. 2022 Best Practices Honoree Dr. Collin Gray, owner of Eyecare of Lehi in Lehi, Utah shares what sparked his interest in advocacy early in his career, and what motivates him to remain involved.

Why is it so important for practitioners to advocate for optometry? And how do you suggest they get started?

I got involved in advocating for the eye care profession very early on in my career. I wanted to play a direct role in advancing the practice of optometry and improving patient care—and outcomes. I find that state associations do most of the heavy lifting when it comes to expanding our scope of practice, so I've invested most of my time and effort there, and I think it's a great way to start.

You mentioned getting involved early, as a young O.D. Who or what first inspired you to do so?

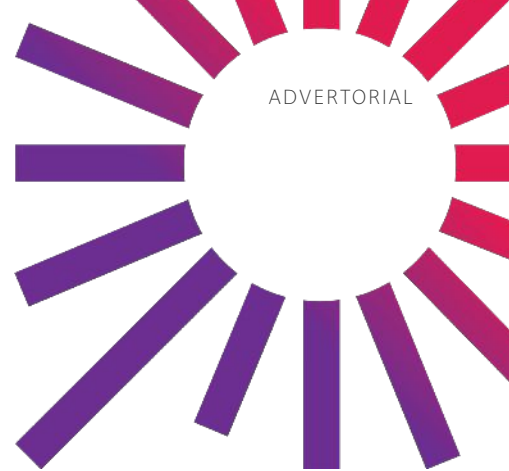
My father—who is also an optometrist—has been involved in legislative advocacy for as long as I can remember. Growing up watching him, it was difficult for me to not build up my own vigor to go out and do the same. When I realized I also wanted to be an optometrist, I felt more inclined to go out and meet with others in the industry and state legislators to fight for changes that help optometrists deliver better care to their patients. Because of my father, I grew up seeing firsthand the importance of advocacy and the impact that using your voice can have on the scope of practice.

What have been some of the biggest benefits of being involved in legislative advocacy so early on in your career?

Networking with other eye care practitioners in the area has been a major—and unexpected—bonus. Especially when I was just starting out, it was a great way for me to meet with other likeminded professionals and hear about the challenges they have faced. It further fueled my passion to advocate for positive change that would directly benefit their practices—and ultimately, mine too. It also helped me to get to know other ECPs within my community. I've even created a list of recent graduates within Utah to which I can refer when other doctors in the area are in need of associates.

Describe a time when optometry in Utah was facing a threat, and how you went about overcoming that obstacle. What were the outcomes?

Just this past year, one of our representatives used a less-than-ideal experience he had with a local ophthalmology practice to sponsor a bill that essentially made contact lenses over-the-counter and non-prescription. For obvious reasons, we had to fight against this. Optometrists from our area came together and testified during the meeting to communicate why comprehensive eye care is so important, how their eye health links to their overall health, and why contact lenses are not a “one-size-fits-all” over-the-counter remedy.



3 TIPS TO GETTING STARTED IN ADVOCATING FOR THE PROFESSION:

- 1 Get Connected.**
Reach out to your state optometric association and ask how you can get involved. Get your name out there and let them know you're available to them.
- 2 Make it a Priority.**
Patient care always comes first, but be sure to make time—at least once a week—to advocate. Whether it's meeting with other doctors or a state senator, make it a regular part of your schedule.
- 3 Be Present.**
Attend your state association meetings. By showing up and getting your face and name out there, you'll be top of mind when your help is needed.

US Estimates of MGD, Dry Eye Prevalence Vary Widely

Authors of a meta-analysis urge experts to develop consensus definitions of the conditions to help clinicians and researchers work with standardized criteria.

While dry eye may seem ubiquitous in eyecare practices, surprisingly little is known about its actual prevalence in the general population. A study recently published in *JAMA Ophthalmology* sought to close this gap, examining the prevalence and incidence of dry eye in relation to meibomian gland dysfunction (MGD).

Since MGD is the hallmark cause of evaporative dry eye, the researchers retrospectively examined 13 studies for data on dry eye and MGD. Analysis indicated that pooled dry eye prevalence in the US population was 8.1%—with estimates in individual studies ranging anywhere from 5.3% to 14.5%—while pooled MGD prevalence was 21.2% but ranged from 10.4% to 55.4%. Annual incidence of dry eye was 3.5% in the population age 18 or older, increasing to 7.8% per year among the 68 or older population. None of the studies reported MGD incidence.

The authors note that the wide range seen in prevalence estimates for dry eye reflects the heterogeneity of clinical and methodological approaches in these studies. Factors that added to uncertainty of a prevalence estimate included variations of study design and setting, varied population characteristics and no standard definition used

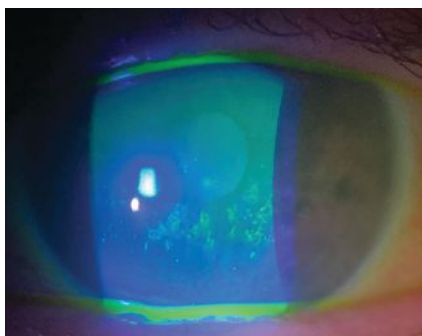


Photo: Pam Theriot, OD

The work concludes that 8.1% of Americans suffer from dry eye, though individual studies pegged it at anywhere from 5.3% to 14.5%.

for dry eye. For instance, one study defined dry eye with relevant diagnostic codes, while another defined it by self-reported diagnosis or symptoms. Part of this high range in prevalence percentage may be in part due to population age differences.

The pooled prevalence may additionally be inflated by studies that are either subject to being unrepresentative of the actual population or at high risk of bias. One example would be a study using data gathered from the Veterans Affairs Administration. While this data may be representative of the veteran population, the predominance of males and the unique exposures that veterans may experience makes the 26.2% prevalence estimate for dry eye an estimation specific only to the popu-

lation of the study conducted, rather than the general population.

Several diagnostic criteria, spanning numerous studies, were included in the dry eye prevalence estimation. However, because these multiple criteria were not replicated across other studies, uncertainty within the prevalence of the underlying population was compounded. With MGD, the range seen in prevalence estimates may be a result of differences in clinical signs used to diagnose the condition.

As the authors point out that other conditions (e.g., glaucoma, AMD) have already received standard diagnostic classifications by expert consensus, they argue that dry eye, too, deserves “a set of working diagnostic criteria for DED is necessary to allow standardization and comparisons in dry eye epidemiological studies.” While this research starts to fill the knowledge gap in a prominent area of eye care, the authors, recognizing the issues with the data, urge clinicians to remember that “the evidence provides uncertain estimates of dry eye burden and highlights the need for further studies that minimize risk of bias and use validated diagnostic criteria.”

McCann P, Abraham A, Mukhopadhyay A, et al. Prevalence and incidence of dry eye and meibomian gland dysfunction in the United States. *JAMA Ophthalmol.* October 27, 2022. [Epub ahead of print].

IN BRIEF

Posterior Segment Alterations Identified in Early-stage Keratoconus.

While the effects of keratoconus (KCN) on the anterior segment are often the focus of clinical studies, new research shines light on the potential impact of the disease on the back of the eye. Even in its early stage, KCN may cause bowing of the lamina cribrosa, subtle peripapillary RNFL thinning and vascular alterations.

The researchers' investigation evaluated 32 eyes with KCN (97% with early-stage disease) and 32 controls. They performed various scans includ-

ing anterior-segment OCT, Placido-disc topography, macular, optic nerve head SS-OCT, SS-OCT-A and a 3D wide glaucoma module.

Patients with KCN appeared to have a reduced peripapillary RNFL thickness compared with controls (104.8µm vs. 110.7µm), as well as reduced nerve radial peripapillary capillary plexus vessel density (46.3% vs. 43.8%). Especially in the temporal sector, these differences were more evident. These two observations were also associated with a higher lamina cribrosa curvature index in KCN patients vs. controls (9.9% vs. 8.5%). In KCN eyes, macular super-

ficial capillary plexus vessel density was also 2.74% lower.

The researchers offered a possible explanation: “Lamina cribrosa may be altered in KCN either due to its collagenous structure or through deformation of the whole posterior sclera and its peripapillary anchor to lamina cribrosa (scleral flange).”

Although the central macular and choroidal thickness appeared to be unaffected by the presence of KCN, the researchers speculated that this may be due to the study's inclusion of only patients with early-stage disease, software-based measurement or the small sample size.

The researchers concluded, “Early-stage KCN may be characterized by a posterior bowing of lamina cribrosa along with a subtle peripapillary RNFL thinning and vascular impairment.” They add that the study's findings support the hypothesis that KCN may be a corneal manifestation of a more generalized eye collagen disease, “which would also affect collagenous structures of the posterior pole, such as peripapillary sclera, lamina cribrosa and retinal vessel wall.”

Li HY, Yang Q, Dong L, et al. Visual impairment and major eye diseases in stroke: a national cross-sectional study. *Eye.* September 21, 2022. [Epub ahead of print].

PROGRESSION IN GEOGRAPHIC ATROPHY IS RELENTLESS AND IRREVERSIBLE¹⁻⁴

While GA progression may appear to move slowly, it can affect your patients faster than you think^{1,4-6}

The consequences of Geographic Atrophy (GA) are too critical to be ignored⁷⁻⁹



IN A MEDIAN OF ONLY 2.5 YEARS, GA lesions encroached on the fovea according to a prospective AREDS study (N=3640)^{2*}



2 OUT OF 3 PATIENTS lost the ability to drive in a median time of <2 years according to a retrospective study (n=523)^{10†}

GA lesions can lead to visual impairment even before they reach the fovea^{1,5,6}



See the effect of GA progression on your patients

*Data sourced from the Age-related Eye Disease Study (AREDS) Report #26—a long-term, multicenter, prospective study examining progression of GA area in a cohort of 3640 patients with signs of early and more advanced forms of AMD.

†A retrospective cohort analysis (N=1901) of a multicenter electronic medical record database examining disease burden and progression in patients in the United Kingdom with bilateral GA secondary to AMD.

BCVA=best-corrected visual acuity.

References: 1. Boyer DS et al. *Retina*. 2017;37:819-835. 2. Lindblad AS et al, and AREDS Research Group. *Arch Ophthalmol*. 2009;127(9):1168-1174. 3. Holz FG et al. *Ophthalmology*. 2014;121(5):1079-1091. 4. Sunness JS et al. *Ophthalmology*. 2007;114(2):271-277. 5. Kimel M et al. *Invest Ophthalmol Vis Sci*. 2016;57(14):6298-6304. 6. Sadda SR et al. *Retina*. 2016;36(10):1806-1822. 7. Singh RP et al. *Am J Ophthalmic Clin Trials*. 2019;(1):1-6. doi:10.25259/ajoc-9-2018. 8. Sivaprasad S et al. *Ophthalmol Ther*. 2019;8(1):115-124. 9. Patel PJ et al. *Clin Ophthalmol*. 2020;14:15-28. 10. Chakravarthy U et al. *Ophthalmology*. 2018;125:842-849.

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Intended for US HCP only.
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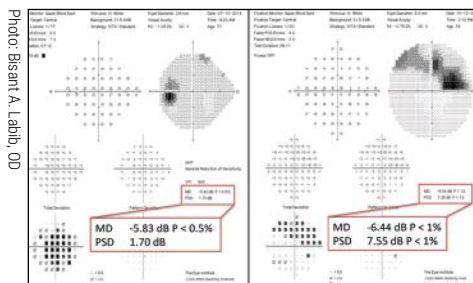
10-2 Best Predictor of Glaucoma Progression

While recent studies reported that baseline 24-2 VF loss in the central 10° provides substantial predictive value for the future rate of glaucomatous VF loss, researchers have yet to investigate the relationship between 10-2 VF test results and future glaucoma VF progression. Researchers recently aimed to close this gap.

Over more than six and a half years, 24-2 VF tests were completed on 394 eyes of 202 subjects (119 primary open-glaucoma patients, 83 glaucoma suspects). Longitudinal 24-2 VF testing was completed every four to six months after baseline 10-2 testing.

While both baseline abnormal 24-2 points within the central 10° and baseline 10-2 VF defects were related to future 24-2 VF progression, regression analysis showed that baseline 10-2 VF loss had more robust and consistent predictive value vs. abnormal central 24-2 points.

“Specifically, we found that when comparing predictive models that did and did not include 10-2 VF variables, the models that included 10-2 VF met-



In many scenarios, 10-2 VF testing (right) can be more sensitive than 24-2 (left).

rics consistently outperformed models without 10-2 metrics,” the authors explained in their paper for *Journal of Glaucoma*. “Further, primary OAG eyes with a baseline 10-2 VF defect had a four-times greater rate of 24-2 MD deterioration vs. eyes with no 10-2 VF defect at baseline, while eyes with abnormal baseline central 24-2 points had only a three-times greater rate of 24-2 MD progression vs. eyes with no abnormal baseline central 24-2 points.”

“Consistent with prior studies, increased age, worse baseline 24-2 VF loss and presence of abnormal baseline central 24-2 points were also identified as predictors of future VF loss in this study, but these variables demonstrat-

ed lesser predictive ability compared with the presence of baseline 10-2 VF loss,” the authors continued. “These findings were maintained even when excluding eyes with moderate or advanced disease, suggesting that central 10-2 VF compromise is an important predictor across the spectrum of glaucomatous disease and that 10-2 VF testing has unique value within baseline glaucoma risk analysis.”

Additionally, this suggests that 10-2 testing provides independent and valuable information for predicting future glaucoma progression that is more precise than using central 24-2 VF information alone.

“While the optimal approach to implementing routine 10-2 VF testing must still be determined, it may be reasonable to obtain baseline 10-2 VF testing within the first few clinic visits to aid initial risk stratification, to create a baseline for future 10-2 VF test comparisons and to verify structure/function relationships,” they concluded. ◀

Sullivan-Mee M, Kimura B, Kee H, et al. Baseline 10-2 visual field loss as a predictor for future glaucoma progression. *J Glaucoma*. October 12, 2022. [Epub ahead of print].

HbA1c Cutoff Point Could Help Detect DR

Individuals with diabetes devote much effort to continuously tracking their hemoglobin A1c (HbA1c) levels, as it dictates many of their health-related decisions and dietary choices. It turns out this metric is also an appropriate care evaluation measurement for diabetes-related eye conditions due to a strong correlation between the test results and disease complications. A recent cross-sectional study aimed to assess whether HbA1c can predict diabetic retinopathy (DR) in type 2 diabetes. It found the prevalence of DR in these patients to be almost 30% with an HbA1c cutoff point of 8.15 for detecting DR as a disabling complication in diabetes.

A total of 168 diabetes patients were selected via the convenience sampling method. Data was collected through questionnaires and laboratory testing. To estimate the HbA1c cutoff point, formal measures of classification performance, model evaluation criteria and a decision tree were employed.

The researchers reported the prevalence of DR among type 2 diabetic patients to be 29.8% among the study participants. The receiver operating characteristic curve and decision tree showed the optimal cutoff point for the HbA1c variable that separated patients with and without DR to be 8.15 with a sensitivity and specificity

of 0.583 and 0.701, respectively. The researchers noted that this high-specific cutoff point can effectively identify patients without retinopathy in the first stage of the disease.

“This cutoff point can be used to guide evidence in several clinical judgments,” they wrote in their paper on the work. “However, additional studies that modify confounding variables are needed to confirm the appropriate level of HbA1c for detecting the development of DR among diabetic patients.” ◀

Setareh J, Hoseinzade G, Khoundabi B, et al. Can the level of HbA1c predict diabetic retinopathy among type 2 diabetic patients? *BMC Ophthalmol*. October 31, 2022. [Epub ahead of print].



KERATOCONUS and CROSS-LINKING

Practice Considerations in Managing Keratoconus and Cross-Linking



Nicole Albright, OD
Clinic Director,
Moses Eyecare Center
An independent optometry
practice in Merrillville, IN

KEY TAKEAWAYS

- Managing keratoconus (KC) meets patients' needs as part of a medical-model optometric practice.
- There is no global period for cross-linking; each follow-up visit is billed as an office visit.
- The progressive KC patients I have referred for cross-linking have become loyal patients.

Many optometrists are shifting towards a medical model of practice, managing chronic conditions with ocular manifestations, including dry eye, glaucoma, and diabetes. Diversifying the services you offer can better meet the needs of your patients.

Managing keratoconus (KC) is a great way to "lean in" to that more comprehensive medical model of optometric care. About 70% of KC patients first present to an optometrist's office,¹ which means

With your medical management and cross-linking referrals, modeling² suggests that patients benefit:

\$8,677

DIRECT MEDICAL COST SAVINGS PER PATIENT

\$43,759

REDUCTION IN LIFETIME COSTS PER PATIENT

1.88

INCREASE IN PATIENT QUALITY-OF-LIFE-YEARS

that we have a unique opportunity to identify this progressive disease and refer patients for the FDA-approved iLink[®] cross-linking procedure in the early stages, before there is permanent vision loss. After treatment, we can continue to address the patient's vision needs over time.

Collaborating with cornea specialists in the care of KC patients has provided comprehensive patient care and strengthened my relationships with ophthalmologists in the community. When they realize that we share a common goal of helping our KC patients, it opens the door not only to specialty contact lens fitting and follow-up care after cross-linking, but to collaboration and referrals in other areas, as well.

Follow-up care after iLink[®] cross-linking is similar to that required for PRK, with five or more visits and one or more contact lens re-fittings in the first year being typical. After that, KC patients will continue to need vision care and annual medical eye care appointments to monitor for any further corneal changes. While the timing and frequency of office visits may vary by patient and at the doctor's discretion, there is no global period for cross-linking. Any necessary post-treatment visits and diagnostic tests, such as pachymetry and topography, are typically billed separately.

I personally find scleral lens fitting and the management of progressive KC patients who are undergoing cross-linking to be among the most rewarding things I do as an optometrist. First and foremost, we offer them a treatment that can slow or halt KC progression. Furthermore,

patients are so very appreciative when you can pinpoint the cause of and address their visual quality problems with contact lenses.

Modeling suggests that iLink[®] cross-linking saves the average patient nearly \$9,000 in direct medical costs and nearly \$44,000 in lifetime costs²—and that doesn't even include the impact on their mental health and well-being. In addition to the cost savings, it is very fulfilling to me to know that I can help protect a young person with early progressive KC from progressing to the advanced stages of the disease, potentially avoiding a lifetime of vision loss and the need for corneal transplant surgery. One study showed a 25% drop in corneal transplants after the introduction of cross-linking.³

Our KC patients are grateful for this care. They will rave about you on social media, refer family and friends—and generally become loyal patients. ■

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2. Lindstrom RL et al. *J Med Econ* 2021;24:410.
3. Godefrooij DA, Gans R, Imhof SM, et al. *Acta Ophthalmol* 2016; 94:675-678.

INDICATIONS

Photrexa[®] Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) and Photrexa[®] (riboflavin 5'-phosphate ophthalmic solution) are indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia following refractive surgery.

IMPORTANT SAFETY INFORMATION

Corneal collagen cross-linking should not be performed on pregnant women. Ulcerative keratitis can occur. Patients should be monitored for resolution of epithelial defects. The most common ocular adverse reaction was corneal opacity (haze). Other ocular side effects include punctate keratitis, corneal striae, dry eye, corneal epithelium defect, eye pain, light sensitivity, reduced visual acuity, and blurred vision.

These are not all of the side effects of the corneal collagen cross-linking treatment. For more information, go to www.livingwithkeratoconus.com to obtain the FDA-approved product labeling. You are encouraged to report all side effects to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

SCAN WITH PHONE

Learn more about iLink
corneal cross-linking here



Glaucoma Unnoticed in One Quarter of African Americans

Noninclusive OCT reference databases are to blame, allowing this population to fall outside what is recognized as the cutoffs for disease diagnosis.

While advancements in glaucoma detection have made the disease easier to track, some diagnostic criteria have not been entirely effective. One new study comparing retinal nerve fiber layer (RNFL) thickness and Bruch’s membrane opening minimum rim width (BMO-MRW) of people from European or African descent found consistently lower diagnostic performance in those of African ancestry. This is even more concerning given the well-documented higher rates of glaucoma in this population.

The prospective study, recently publishing in *American Journal of Ophthalmology*, included analysis of 382 eyes from glaucomatous patients and 94 healthy eyes from controls. Global and sectoral RNFL thickness and BMO-MRW were measured with Spectralis OCT (Heidelberg Engineering) scans. Six different diagnostic criteria were used to compare the two groups, including: global measurement below the fifth or first percentile, greater than or equal to one of the six sector measurements below the fifth or first percentile, and superotemporal and/or inferotemporal measurement below the fifth or first percentile. The sensitivities and specificities of the measurements were then compared.

The researchers found that superotemporal and/or inferotemporal RNFL below the fifth percentile performed

best as an indication of glaucoma within the nerve fiber-based classifications, displaying 89.5% sensitivity and 87.2% specificity, and this applied to both ethnic groups. For those of African descent, sensitivities and specificities for superotemporal and inferotemporal layer thickness, as well as minimum rim width measurements below the fifth percentile, were all lower than in European descent individuals.

As a result, diagnostic performance of RNFL and BMO-MRW metrics was consistently lower in the African descent group. The authors specifically point out that the minimum rim width criteria may fail to detect as much as up to one-third of glaucomatous eyes in individuals of African descent. They believe this might stem from a greater optic disc area, larger cup-to-disc ratio and bigger BMO area. Even further, they caution that printout of this criterion should be interpreted carefully, with up to one-fourth of those of African descent displaying a normal OCT.

The authors also mention that it is not standard to take race into account when determining a normal range for OCT measurements, despite multiple studies that suggest optic nerve parameters exhibit differences across ethnicities. Optic disc size is one parameter adjusted for in Spectralis, although this adjustment alone cannot account for the differences of diagnostic accuracy



Photo: Getty Images

OCT diagnostic criteria often don't consider minorities such as African Americans, which may contribute to missed or delayed glaucoma diagnosis, study finds.

of thickness layer and rim minimum rim width of African descent group.

Because of the disparities demonstrated in all these criteria, the authors argue that database reference information should be examined for accuracy in diverse ethnic populations and that a larger, ethnicity-specific reference database is needed in OCT assessment. When considering application to practice, the authors caution, clinicians should be careful when using OCT since RNFL thickness and especially BMO-MRW criteria “are not adequate for diagnosing glaucoma in individuals of African descent which may lead to misidentification of some glaucomatous eyes and failure to detect early glaucomatous damage in such individuals.”

El-Nimri N, Moghimi S, Nishida T, et al. Racial differences in detection of glaucoma using retinal nerve fiber layer thickness and Bruch’s membrane opening minimum rim width. *Am J Ophthalmol*. October 28, 2022. [Epub ahead of print].

IN BRIEF

■ Majority of Retinal Tears Post-PVD Develop After Six-Week Follow-up.

Researchers recently examined the long-term incidence and timing of delayed retinal tears following symptomatic acute posterior vitreous detachments (PVDs) without concurrent tears and also identified factors that may increase the risk of developing tears.

A total of 389 patients with acute, symptomatic PVD without concurrent retinal tears were examined. Kaplan-

Meier analysis showed that 7.39% of eyes developed delayed retinal tears by 6.24 years after initial PVD diagnosis, with many developing tears well after a typical six-week follow-up. Of these tears, 50% occurred within 4.63 months of PVD diagnosis and 63.46% occurred within one year of diagnosis.

Most previous studies had a short maximum follow-up period of just six weeks. “Our study, on the other hand, included a much longer follow-up period of over six years, and the Kaplan-Meier analysis captures patients who may have been noncompliant with

follow-up and therefore allows us to conclude that while 45% of delayed tears occurred before six weeks, the majority of tears (55%) were, in fact, found after six weeks, accounting for 2.83% of all eyes that experienced an acute, symptomatic PVD,” the study authors explained. “This suggests that previous studies with similar definitions for acute, symptomatic PVDs could have underestimated the actual incidence of delayed retinal tears.”

Lattice degeneration was found as a likely risk factor for delayed tears, given the retinal stretching and

thinning. Lens status and age were not risk factors, and in contrast with previous studies, this study found that refractive error, sex, race and ethnicity were not associated with delayed retinal tears.

These findings can guide clinicians in establishing optimal follow-up protocols for patients with acute, symptomatic PVD, the authors concluded.

Jindachomthong KK, Cabral H, Subramanian ML, et al. Incidence and risk factors for delayed retinal tears following an acute, symptomatic posterior vitreous detachment. *Ophthalmol Ret*. October 25, 2022. [Epub ahead of print].

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**ON THE PATH TO
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Amniotic membrane image not to scale, enhanced to show detail.

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CPT CODE 65778:
Placement of amniotic membrane on the ocular surface without sutures

References: 1. Walkden A. Amniotic membrane transplantation in ophthalmology: an updated perspective. *Clin Ophthalmol.* 2020;14:2057-2072. 2. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf.* 2017;15(3):276-283. 3. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf.* 2017;15(3):575-628.

*There are no specific FDA indications for the product.

This information does not guarantee payment and is not legal advice.

It is the provider's responsibility to check for proper coding and billing.

Before use, please refer to Information for Use (IFU) package insert.

HRT Increases Risk of Cataract Surgery in Women

Women have a higher risk of cataract, with studies showing that hormones may play a significant role. Researchers of a recent study aimed to investigate the effects of hormonal contraception and hormone replacement therapy (HRT) use on the risk of cataract surgery among Australian women. They also

evaluated whether the association between exogenous hormone use and cataract surgery risk is affected by other demographic, socioeconomic and lifestyle factors.

In total, 91,760 females between the ages of 45 and 65 with no history of cataract surgery were included. Past and present users of HRT had a 22% and 14% increased risk of cataract surgery, respectively. A dose response with longer HRT use resulted in a larger increase in cataract surgery.

The authors also identified a marginally protective effect of hormonal contraceptive use on cataract surgery risk. For HRT non-users, hormonal contraception use was associated with a 13% lower risk of cataract surgery.

“To be noted, a high proportion of hormonal contraception users turned to use HRT after menopause (34.9% in this cohort); therefore, it is possible

that the effects of HRT and hormonal contraception on cataracts are counteracted,” the authors explained.

Differences in the dosing and composition of hormone administration might partly explain the opposite effects of HRT and hormonal contraception. “Contemporary contraceptives are mostly used in reproductive age and contain fairly high estrogen doses compared with HRT, which is mostly used during and after menopause,” the authors noted. “It’s been reported that different doses of estrogen have opposite effects on the lens.”

Smoking, drinking and minimal physical activity further increased the risk of cataract surgery. ◀

Zhang J, Shang X, Liu Z, et al. Exogenous hormone use and the risk of surgically treated cataract: evidence from 91,760 female participants in the 45 and Up study. *Acta Ophthalmol.* September 24, 2022. [Epub ahead of print].



Photo: Gleb Sukhowski, OD

Researchers found a dose response, with higher cataract surgery rates among those with longer duration of HRT use.

Visits for Flashes and Floaters Strain Emergency Services

Researchers hope a more informed triage strategy can increase efficiency for the healthcare system.

Optometrists and ophthalmologists know the visual symptoms brought on by flashes and floaters may be annoying, but most often are not concerning as a matter of eye health. However, to patients these phenomena can be quite troubling, enough so to prompt emergency visits.

Researchers recently found that patients who had flashes and floaters for less than two weeks, were 45 or older and were seen at an urgent care center were more likely to require further consultation with ophthalmology emergency services. Headache and neurological symptoms were negatively associated with further consultation.

Of 6,590 primary eye-related visits to general emergency services, 10.4% involved symptoms of flashes and/or floaters. The consultation rate to ophthalmology emergency services for flashes and/or floaters was 89%. Logistic regression modeling identified

symptoms \leq two weeks (OR: 8.0), age \geq 45 (OR: 2.4), an urgent care center setting (OR: 2.7), headache (OR: 0.22) and neurological symptoms (OR: 0.1) as variables predictive of ophthalmology emergency service consultation. In the cohort of patients who were \geq 45, had acute symptoms and lacked headache and neurological symptoms, 94% consulted ophthalmologic emergency services. “Patients with headache and neurologic symptoms may be more likely to have nonocular diagnoses such as migraine or stroke,” the researchers noted in their paper.

The mean time from triage to discharge in general emergency services for flashes and/or floaters was 2.43 hours, and the mean cost per visit was \$139.11 CAD. Patients who consulted ophthalmic emergency services waited a total of 1,345 hours in general emergency services and accounted for \$81,879.70 CAD in costs.

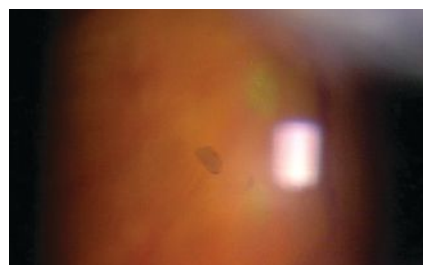


Photo: Nathan Lightizer, OD

One in 10 visits to emergency medicine providers for eyecare services centers on flashes and/or floaters, study says.

“We hope this research will help inform future practice patterns when it comes to the triage of eye-related complaints by contributing to the knowledge needed to guide prospective studies on innovative care pathways appropriate for local health systems,” the researchers concluded. ◀

Shen C, Liu A, Farrokhyar F, et al. The burden of flashes and floaters in traditional general emergency services and utilization of ophthalmology on-call consultation: a cross-sectional study. *BMC Ophthalmol.* October 4, 2022. [Epub ahead of print].

— THE — DANGER CAN BE HARD TO SEE. LOOK CLOSER.

For patients with Graves' disease (GD), Thyroid Eye Disease (TED) may be hiding in plain sight.^{1,2}

Up to 50% of patients with GD may develop TED, a separate and distinct disease which can progress if left untreated. Look out for the early signs and symptoms³⁻⁶:

- Proptosis
- Diplopia
- Dry eyes
- Sensitivity to light
- Grittiness
- Pain or pressure behind the eyes

If you identify new or changing signs or symptoms, consult with an eye doctor who specializes in TED right away.^{1,7}



Visit [TEDImpact.com](https://www.tedimpact.com) to find a TED Specialist

References: 1. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. *J Ophthalmol.* 2015;2015:249125. 2. Bothun ED, Scheurer RA, Harrison AR, Lee MS. Update on thyroid eye disease and management. *Clin Ophthalmol.* 2009;3:543-551. 3. Bahn RS. Graves' ophthalmopathy. *N Engl J Med.* 2010;362(8):726-738. 4. Bartalena L, Krassas GE, Wiersinga W, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab.* 2012;97(12):4454-4463. 5. Patel A, Yang H, Douglas RS. A new era in the treatment of thyroid eye disease. *Am J Ophthalmol.* 2019;208:281-288. 6. Ponto KA, Pitz S, Pfeiffer N, Hommel G, Weber MM, Kahaly GJ. Quality of life and occupational disability in endocrine orbitopathy. *Dtsch Arztebl Int.* 2009;106(17):283-289. 7. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid.* 2016;26(10):1343-1421.

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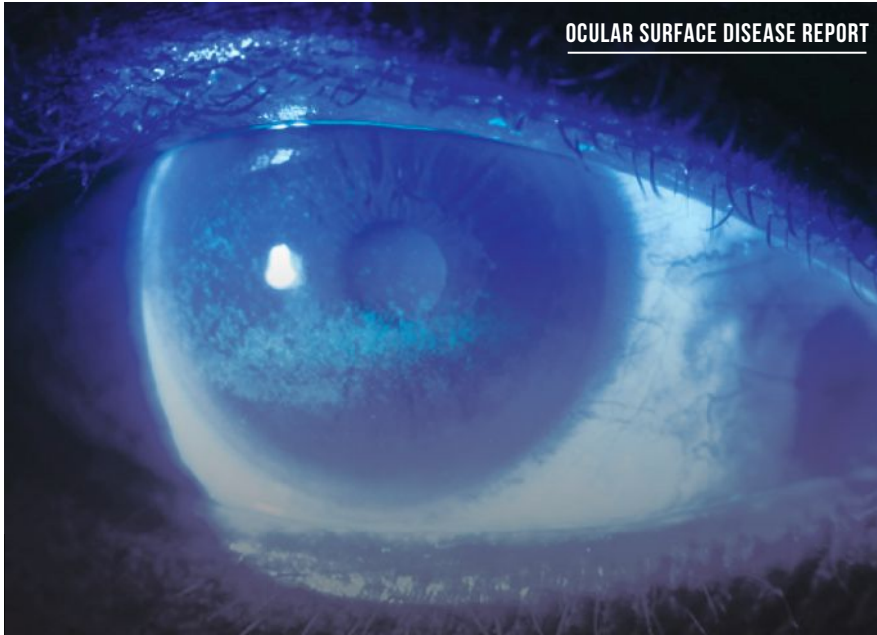
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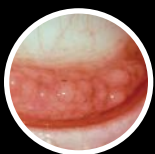
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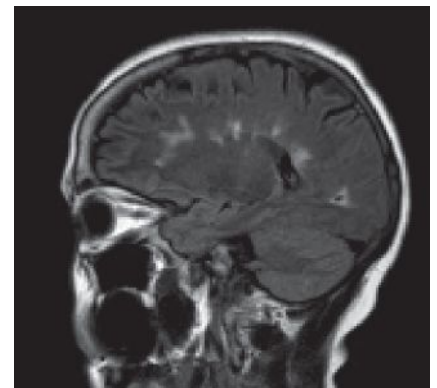
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Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.



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East Hanover, New Jersey 07936-1080



Not an actual patient.

Important Safety Information (cont)

- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information about XIIDRA[®], please refer to the brief summary of Prescribing Information on adjacent page.

†Pivotal trial data

The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0-4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0-100).¹

Effects on symptoms of dry eye disease: A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials.¹

Effects on signs of dry eye disease: At day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 of the 4 studies.¹

References: **1.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **2.** Data on file. Fingertip Formulary[®] as of 07/2022. Novartis Pharmaceuticals Corp; July 2022.

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XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use

Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation [see *Adverse Reactions (6.2)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see *Contraindications (4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. 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.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported [see *Contraindications (4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce

teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear [see *Clinical Pharmacology (12.3) in the full prescribing information*].

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from pre-mating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low [see *Clinical Pharmacology (12.3) in the full prescribing information*]. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

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

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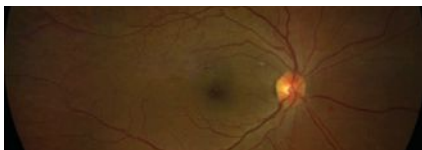
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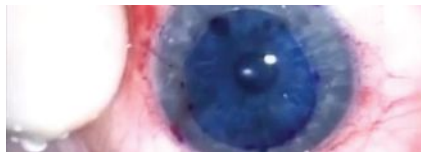
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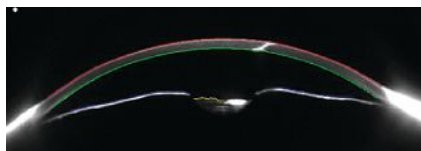
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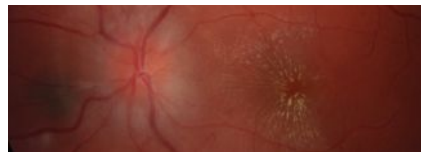
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We Welcome Your Comments

Feedback from the community provides important insights about clinical practice. If you would like to share your thoughts on the topics discussed in this issue—or the wider field of optometry at large—please write to: editor@reviewofoptometry.com

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Business Offices

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PUBLISHER

MICHAEL HOSTER

(610) 492-1028

mhoster@jobson.com

SENIOR MANAGER, STRATEGIC ACCOUNTS

MICHELE BARRETT

(610) 492-1014

mbarrett@jobson.com

REGIONAL SALES MANAGER

JONATHAN DARDINE

(610) 492-1030

jdardine@jobson.com

PRODUCTION MANAGER

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(212) 274-7057

faponte@jobson.com

PRODUCTION MANAGER

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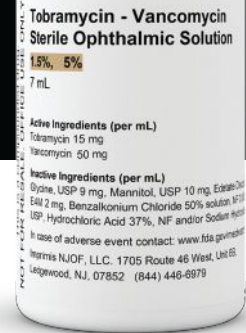


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(610) 492-1006 • jpersico@jobson.com

SENIOR EDITOR

JULIE SHANNON
(610) 492-1005 • jshannon@jobson.com

SENIOR ASSOCIATE EDITOR

CATHERINE MANTHORP
(610) 492-1043 • cmanthorp@jobson.com

SENIOR ASSOCIATE EDITOR

MARK DE LEON
(610) 492-1021 • mdeleon@jobson.com

ASSOCIATE EDITOR

LEANNE SPIEGLE
(610) 492-1026 • lspiegle@jobson.com

ASSOCIATE EDITOR

RACHEL RITA
(610) 492-1000 • rrita@jobson.com

SENIOR SPECIAL PROJECTS MANAGER

JILL GALLAGHER
(610) 492-1037 • jgallagher@jobson.com

SENIOR ART DIRECTOR

JARED ARAUJO
jaraujo@jobson.com

GRAPHIC DESIGNER

LYNNE O'CONNOR
lyoconnor@jobson.com

DIRECTOR OF CE ADMINISTRATION

REGINA COMBS
(212) 274-7160 • rcombs@jobson.com**Clinical Editors**

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BY JACK PERSICO
EDITOR-IN-CHIEF
OUTLOOK

A Warrior for Wellness

Stuart Richer taught us to anticipate and avoid, rather than merely react to, diseases. His patients—and profession—are healthier for it.

Another month, another loss. In late October, just as this year's Academy of Optometry meeting was getting into full swing, news broke that Stuart Richer, OD, PhD, had passed away. With the recent death of Art Epstein still on our minds, we had to process the news of another lion of the profession leaving us.

Dr. Richer was a tireless advocate for the notion that health and wellness interventions are integral parts of optometry's public mandate. During his time as president of the Ocular Wellness and Nutrition Society (OWNS), he championed that idea and worked hard to bring it into the mainstream. Like his predecessor at OWNS, Jeff Anshel, and successor, Julie Poteet, Dr. Richer took up the charge to overcome the misapprehension that wellness is a niche area of eye care or something nice to address with patients "when there's time." What could be more fundamental to health-care than a mindset of prevention? As with so many other things, health problems are incalculably harder to tackle after they've taken root.

We have our work cut out for us, it seems. A new estimate of AMD prevalence, just published in *JAMA Ophthalmology*, informs us that 20 million Americans currently have the disease. Obviously, that number will only rise. Thankfully, the mindset that optometrists can play an active role in mitigating this disease is no longer controversial, in no small measure because of Dr. Richer.

"Stu, as he is affectionately known to many, was a brilliant, widely respected luminary, innovator, researcher, professor and compassionate

human who has changed the way we think about taking care of patients," wrote his friend and colleague Dorothy Hitchmoth, OD, in a tribute on her LinkedIn page. "Dr. Richer's contributions to the science of vision loss prevention cannot be understated. His clinical and laboratory discoveries have given hope that vision loss from age-related macular degeneration and other causes of visual impairment and poor health can be prevented."

I had the privilege of working with Dr. Richer on a recurring supplement to this magazine called *Wellness Essentials for Clinical Practice*, produced in conjunction with OWNS, and always admired his ability to communicate complex ideas in a simple way. When someone with such depth of expertise as Dr. Richer possessed commits to sharing it with their colleagues, the entire field expands and grows.

More so that most professions, optometry has always moved forward on the backs of the innovators who brought their priorities and persistence to it. From the early days of Charles Prentice and Andrew Cross to more recent icons like Larry Alexander and Brien Holden, optometry has advanced when someone steps up and shows others what the profession could and should become next. Stu certainly fits that mold.

"He will be most known for his compassion, empathy and respect for patients and providers alike," Dr. Hitchmoth concluded in her remembrance of Dr. Richer. "Undoubtedly, his work forms the foundation for a holistic approach within our profession toward the prevention of vision loss, function and life." ■



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BY PAUL M. KARPECKI, OD
CHIEF CLINICAL EDITOR

THROUGH MY EYES

A Different Approach

Can emulating the dental model improve how we treat OSD?

There are many similarities between eye care and dentistry. Why am I bringing up dentistry in an optometry magazine? Preventing ocular surface disease (OSD) is imperative to keeping our patients' eyes healthy, just as preventing gum disease is imperative to keeping mouths healthy. Does this mean a preventative model for OSD is possible?

ODs and Dentists: The Parallel

Beginning with diagnostics, dentists use mirrors and magnifiers to closely observe the mouth, but especially the gingiva or gums. Likewise, we need to spend more time not just observing the cornea and internal eye, but truly scrutinizing the eyelids.

Dentists use X-rays, and we can use imaging ranging from meibography (LipiScan, Oculus) to slit lamp cameras (Haag-Streit BQ900) to advanced diagnostics such as tear film imaging (AdOM) and dry eye analysis (Oculus). Dentists have eye whitening options and ODs can consider eye whiteners that don't constrict arteries, like Lumify (Bausch + Lomb). Finally, dental patients with morning symptoms typically have bruxism (teeth grinding) and eyecare patients with morning symptoms have inadequate lid closure.

Examining the Eyelids

To effectively manage OSD, shift your focus from the ocular surface to the eyelid. The reason is that 86% of dry eye disease (DED) involves meibomian gland dysfunction (MGD).¹ Some clinical signs to observe include a

frothy tear film, a sheen on the lids indicative of biofilm, collarettes or a volcano sign where debris is present at the base of the lashes indicating *Demodex* or staphylococcal blepharitis. Capped glands, posteriorly placed meibomian glands and thickened or scalloped eyelid margins are all key signs.

“
To effectively manage OSD, shift your focus from the ocular surface to the eyelid.
”

Next, have the patient look down, increase magnification and scan the upper eyelid margin. Finally, express the meibomian glands. Not doing this is akin to saying you want to manage glaucoma but don't want to observe the optic nerve or manage macular degeneration without looking at the macula.

Plaque and Biofilm

In the world of dentistry, the term for biofilm is *plaque*. Dentists or hygienists spend the majority of their time removing biofilm because it leads to diseases like gingivitis and eventually loss of teeth. We should do the same by focusing on microblepharoexfoliation (BlephEx) and debridement (Bruder), which may prevent meibomian gland loss or atrophy. Dentists recommend patients continue to work on preventing plaque through brushing and flossing, and we can recommend lid scrubs from (Ocusoft) and Bruder mask hydrating compresses.

Morning Symptom Treatments

Dental patients who have morning symptoms are often diagnosed with bruxism, and the solution is an overnight bite guard. In eye care, patients with morning symptoms almost always have inadequate lid seal issues, and the treatment involves overnight lid seals (SleepTite).

Prevention and Pre-scheduling

An area where optometrists and dentists diverge is in disease prevention. Dentists treat plaque every six months to prevent loss of tissue and teeth. Perhaps we should consider this to prevent meibomian gland atrophy and chronic DED. While it might be a stretch for us to treat patients without signs or symptoms, start treatment when signs are first evident, including MGD-based on expression or froth in the tear film, blepharitis or biofilm, with signs including a sheen, collarettes or debris on the lashes, or inadequate lid closure.

The second thing we can learn from dentistry is to preappoint patients. Dentist offices know how essential it is to reschedule a patient every six months. In our case, we need to make the decision based on the level of disease, such as DED vs. MGD, but it's important to schedule that patient for a follow-up exam so we can avoid the progression of OSD.

It's important to take all of the steps necessary to prevent ocular surface disease or at least manage it properly, even if it means taking a different approach and shifting your focus. So, maybe it is possible to follow this model and have not just happy patients, but happy optometrists! ■

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About
Dr. Karpecki

Dr. Karpecki is the director of Cornea and External Disease for Kentucky Eye Institute, associate professor at KYCO and medical director for the Dry Eye Institutes of Kentucky and Indiana. He is the Chief Clinical Editor for Review of Optometry and chair of the New Technologies & Treatments conferences. A fixture in optometric clinical education, he consults for a wide array of ophthalmic clients, including ones discussed in this article. Dr. Karpecki's full disclosure list can be found in the online version of this article at www.reviewofoptometry.com.

Get more out of your eyedrop bottles



Have you ever heard patients complain about their eyedrops? Maybe they ran out before the end of the month and had to wait for insurance to cover their next refill, or their eyes felt flooded with too much fluid? Have you noticed how much of the drop runs down your patients' faces when you're trying to dilate their eyes?

That's because eyedrops are too large for the eye to absorb. The Nanodropper Adaptor has solved this problem. Here's how it works!

What's the problem with eyedrops?

They're too big! **About five times too big, to be exact.** This means 80% of every eyedrop (and thus, every bottle) is wasted due to overflow and/or systemic absorption. This waste contributes to financial barriers to care, and clinical research has shown that oversized drops increase both local and systemic side effects!

How does Nanodropper help?

Pretty simple — by reducing the size of eyedrops to just what the eye can absorb! Smaller drops reduce waste and the cost of in-clinic and prescription eyedrops, and research has shown smaller drops minimize local and systemic side effects.

The Nanodropper is compatible with most of your commonly used in-office drops like Phenylephrine, Paremyd, OTC drops like Lumify, and expensive glaucoma medications like Rhopressa, Rocklatan, Vuity, and many more!



The Nanodropper Adaptor is quickly becoming the new standard of care, not only addressing patient concerns and challenges, but also a larger societal medical waste issue. It's not just a want to have, but a need to have.

-Robert Wooldridge, OD, of the Eye Foundation of Utah and advisor for Nanodropper



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The Nanodropper is the only FDA-listed, volume-reducing adaptor for eyedrop bottles designed to deliver precisely the amount of fluid the eye can absorb. Smaller drops reduce the waste and cost of in-clinic and Rx formulations while minimizing local and systemic side effects.



Food for Thought

Eat what you want—and hope you don't live long enough to deal with the consequences.

This is not a “how to be a super successful optometrist” white paper. I could never write a paper on that because my definition of someone “super successful” is simply “do something you like to do and get someone to pay you to do it.” As Oprah reminded us, money only gets rid of one problem.

“**Food is an integral part of our day. We want our staff members (and ourselves) to have energy and be focused, not bloated and hungry.**”

No, this is about hunger. I myself am actually starving. For some reason my lovely wife, Renee, feeds me like she doesn't want me to drop dead of a heart attack. She apparently only wants me to starve to death. I guess that's her love language.

Food is an integral part of our day. We want our staff members (and ourselves) to have energy and be focused, not bloated and hungry. So why do we fill our break rooms with donuts, kolaches, cookies, chips, pies, cakes and, if we're lucky enough, pizza, burritos and tacos? If you Google the top 50 things that kill people, these are all on the list.

Staffers cram as many combinations of these deadly substances into their mouths as they can between patients and wonder why we find them asleep in the bathroom stalls. Don't ask me

how I know. Ask me about our secret in-office camera surveillance system instead.

We should offer salad, broccoli, cauliflower florets, sliced tomatoes and an assortment of anchovies instead. Why don't we? Easy. Because we would have a lot of people quitting. Carbs instantly become sugar, sugar is addictive and addicts always come back. Always.

Now, I know you health nuts out there will complain that, prepared properly, vegetables are actually very tasty and satisfying to even the most sugar-addicted among us. I agree. Carrot cake is a great example of that, especially if you add about three inches of cream cheese icing on top.

Enough about you. Back to me. I am still hungry. I've made several observations regarding how optometrists and food coexist.

1. An optometry office should at least have a skeleton crew operating during the lunch break, not the eye doctor. They must eat no matter the emergency.
2. Upwards of 75% of optometrists eat lunch at a restaurant every day. At least 30% eat at the same

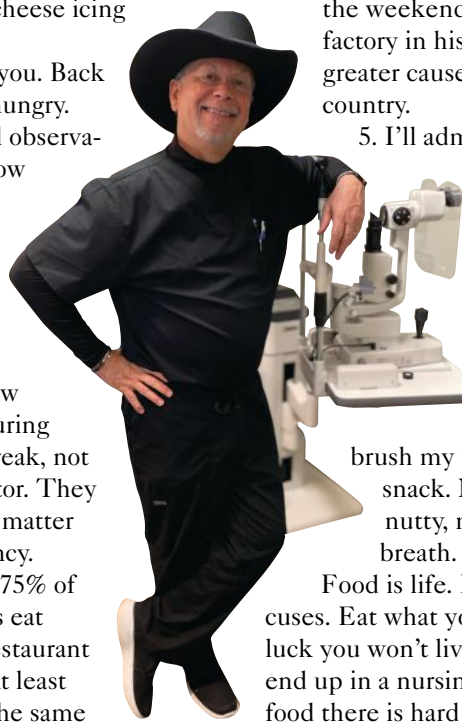
exact restaurant every day. Of those, 30% eat the same thing at the same restaurant every day. The rest are more adventurous, bravely ordering a whole different burger, perhaps with a whole different cheese, for example.

3. A recent survey found that the three most popular foods are beetles, grubs and ants. Turns out this was from interviews with aardvarks and optometrists who offer free eye exams.
4. Food from sales reps and cataract surgeons used to be really common, but somebody woke up some 80-year-old senator who decided that these were like payola or bribes and banned them from the healthcare world. Then he flew to a private beach in the Bahamas to make sure the lobbyists who paid his way and wined and dined him for the weekend would build a factory in his state. There is no greater cause than service to our country.

5. I'll admit I snack at work.

After all, Renee isn't there, and I love her too much to upset her. I like cashews and peanuts. I like beef jerky. I like sardines. Hey, I make sure to brush my teeth after every snack. Nothing better than nutty, meaty, fishy mint breath.

Food is life. Don't make excuses. Eat what you want. With any luck you won't live long enough to end up in a nursing home. I hear the food there is hard to chew. ■



About Dr. Vickers

Dr. Vickers received his optometry degree from the Pennsylvania College of Optometry in 1979 and was clinical director at Vision Associates in St. Albans, WV, for 36 years. He is now in private practice in Dallas, where he continues to practice full-scope optometry. He has no financial interests to disclose.

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BY BISANT A. LABIB, OD

THE ESSENTIALS

A Sweet Measurement

Hemoglobin A1c is a good indicator of glycemic control.

Diabetic eye exams are a routine part of any optometric practice and are encountered daily. Oftentimes, we ask the same pertinent history elements that help us determine the extent of a patient's control of their diabetes so that we can best manage their ocular health and have somewhat of an expectation of their risk and progression.

Two of these historical elements are numerical: the patient's last fasting blood sugar and hemoglobin A1c (HbA1c). Understanding the difference as well as the significance of both is important in assessing the overall clinical picture for the diabetic patient.

Diagnosis Criteria

It has long been established that a criterion for the diagnosis of diabetes mellitus includes last fasting blood sugar level, specifically a value greater than or equal to 126 mg/dL or a two-hour oral glucose tolerance test greater than or equal to 200 mg/dL. However, in 2010, the American Diabetes Association recognized a new diagnostic criterion using HbA1c. This test offers many advantages over the rest and is now measured routinely for all diabetics. Since it is a newer classified criterion, it is necessary to understand how this measurement works and what it means for our patients.^{1,2}

Chemical Structure

Hemoglobin (Hb) is the oxygen-carrying protein found within human red blood cells and is essential for oxygen transportation to sustain life. In terms of its chemical structure, Hb is a metalloprotein tetramer—meaning it is an iron-containing compound composed of four protein chains. The most abundant form of Hb within the human circulatory system is HbA. This form is made up of two alpha chains and two beta chains, constituting 97% of all healthy adult hemoglobin.²

Additional minor forms of Hb arise due to posttranslational modification of the parent Hb A compound. Of these minor Hb, the most common form is the infamous HbA1c, which makes up the approximate 3% remaining of the total Hb in a healthy adult.^{2,3} HbA1c is formed from the parent Hb A com-

pound through a process called glycation. When glycation occurs, a glucose molecule is nonenzymatically attached to the parent Hb A compound, thus converting Hb A to HbA1c. As red blood cells contain both Hb A and glucose molecules, the process of glycation to form HbA1c occurs spontaneously throughout the life span of the cell, which is 120 days.

Also, because the process is non-enzymatic, the amount of glycation is directly proportional to blood glucose levels—high levels of glucose will yield higher concentration of HbA1c. This means that generally, for every 30mg/dL increase in blood glucose, a 1% increase in HbA1c concentration results.

Clinical Significance

These features make HbA1c measurements excellent indicators of long-term glycemic control. It is an overall better index of general, more long-term control and is less subject to acute shifts in blood glucose levels due to acute illness or stress. As such, HbA1c is used in clinical practice both to diagnose and prognosticate. Patients with a HbA1c greater than or equal to 6.5% meet criteria for a diagnosis of diabetes mellitus while those with values greater than or equal to 5.7% but less than 6.5% are classified to have prediabetes or impaired fasting glucose.^{2,4}

Another advantage is that patients do not need to fast prior to their HbA1c measurement for an accurate result. In terms of prognostication, every 1% reduction in HbA1c value has been associated with a 37% reduction in the risk of developing diabetic retinopathy.⁴



Patient with high Hb A1c and nonproliferative diabetic retinopathy.

About
Dr. Labib

Dr. Labib graduated from Pennsylvania College of Optometry, where she now works as an associate professor. She completed her residency in primary care/ocular disease and is a fellow of the American Academy of Optometry and a diplomate in the Comprehensive Eye Care section. She has no financial interests to disclose.

TABLE 1. FACTORS THAT CONTRIBUTE TO FALSE HB A1C READINGS

A1c Measurement	Falsely High	Falsely Low
Conditions	Iron deficiency anemia, B12 and folate deficiency anemia, asplenia	Blood loss, hemolytic anemia, splenomegaly, end stage renal disease
Substances	Alcohol, opioids, vitamin C	Ribavirin, interferon-alpha, vitamin E

Keep an Eye Out

As many advantages as there are to this tool, there are some instances where it can be inaccurate. One important caveat to bear in mind is that HbA1c measurements are a time-dependent, weighted mean of a patient's blood glucose levels over the past three months. Thus, more recent blood glucose trends influence a patient's HbA1c measurement more than the more remote trends. As a result, if a patient, for example, had excellent blood glucose control during months one and two but poor control during month three due to steroid course for uveitis, his HbA1c measurement would be disproportionately elevated by the more recent blood glucose trend in month three.²

There are also several instances in which HbA1c measurements can be falsely high or low. Since the measurement is directly related to red blood cells, any condition that either prolongs or shortens the life span of a red blood cell can yield an inaccurate measurement. Some conditions resulting in a falsely elevated HbA1c include iron deficiency, B12 and folate deficiency anemias and asplenia. Chronic alcoholism, use of opioids and vitamin C supplements may also yield similar effects. Conversely, shortened red blood cell life or turnover can result in a falsely lowered HbA1c. These conditions include acute or chronic blood loss, hemolytic anemia, splenomegaly, end stage renal disease and

even pregnancy. Substances that do the same include vitamin E, ribavirin and interferon-alpha.¹

Takeaways

The ocular complications of diabetes are well-established, including ocular surface disease, corneal complications, increased risk for infection, cataracts, retinopathy and macular edema.⁵ As such, paying close attention to diabetic control in our patients is vital because it may serve as a predictor of disease or dictate how closely they should be followed. The HbA1c is a helpful element in this scenario. ■

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EDITED BY PAUL C. AJAMIAN, OD

CLINICAL QUANDARIES

A Hiccup or a Burp?

Some may hesitate, but this technique can provide immediate pressure lowering and symptomatic relief to the patient.

Q I am seeing a one-day post-op cataract patient that has moderate corneal edema, mild discomfort, and an IOP of 40mm Hg. What should I do?

A To answer this timely question, I've asked Brian Den Beste, OD, and his son Kyle Den Beste, MD, to respond. The father-son team work at Den Beste Eye Consultants in Orlando.

"I think it's appropriate to explain why this happens," says Kyle Den Beste, MD, a cornea and cataract surgeon. "Some patients are just prone to have elevated postoperative pressures, usually because their trabecular meshwork is compromised."

However, the majority of patients have a pressure spike because of retained viscoelastic material. Like all surgeons, he uses viscoelastic compounds during cataract surgery for a host of reasons, but most often to protect the corneal endothelium during phacoemulsification. "The compound is invisible and despite our best efforts to remove all of it, sometimes a small amount gets left behind in the angle and blocks aqueous outflow," Dr. Den Beste notes.

To safely lower pressures that are 35mm Hg or under, Brian Den Beste, OD, will typically increase the topical steroid dosage and add either timolol or timolol/dorzolamide in combination, because the intraocular pressure (IOP) elevation is from both a mechanical and an inflammatory process. "If the IOP is above 35mm Hg, we typically burp the wound," he says.

"I always tell optometrists that comanagement of post-op care is great for patients, but in instances like this if the referring doctor is not comfortable with lowering the pressure, there is no shame in sending the rare patient back for a burping," Kyle Den Beste, MD, points out.

Having worked with Orlando area optometrists for over 35 years, Brian Den Beste, OD, has always been impressed with not only their compassion to learn but also their total commitment to patient safety. "I have burped many incisions over the years without complication, as have a number of my colleagues, but not everyone feels comfortable with the technique," he notes.

Procedure of Choice

Burping incisions is relatively simple and done at the slit lamp. Controlling the lids with your off hand is key. Just like in foreign body removal, start

with three drops of proparacaine and a drop of antibiotic. Some pretreat the eye with Betadine (povidone-iodine 5%).

Kyle Den Beste, MD, recommends applying pressure with a blunt instrument adjacent (toward the sclera) to the paracentesis wound as you observe the aqueous outflow. The wound is like a trap door and mild pressure on the outside of the wound allows a quick escape of fluid.

"The instrument the two of us prefer is called an Ellis Spud," says Brian Den Beste, OD. "I use it for foreign body and rust ring removal."

The spud works like a small spoon, and its back side makes a perfect smooth tool to apply pressure to the trap door incision. Some prefer a 30-gauge needle or anything with a flat surface.

Be prepared that some incisions may be harder to burp than others. If that is the case, Dr. Den Beste will go to the main wound to achieve the necessary pressure relief.

Once the procedure is complete, perform a quick IOP check to ensure a safe pressure has been achieved. Often the IOP will drop from over 40mm Hg to 12mm Hg instantaneously. We apply a drop of antibiotic, and typically see the patient back in two to three days. It's rare to observe a subsequent elevated IOP, but it happens on occasion.

"Patients with discomfort feel immediate relief, and it's amazing how quickly microcystic corneal edema resolves," Kyle Den Beste, MD, says. "Still, in patients that are more at risk, such as those with pre-existing glaucoma, we are more aggressive with prescribing pressure medications or short-term oral acetazolamide." ■

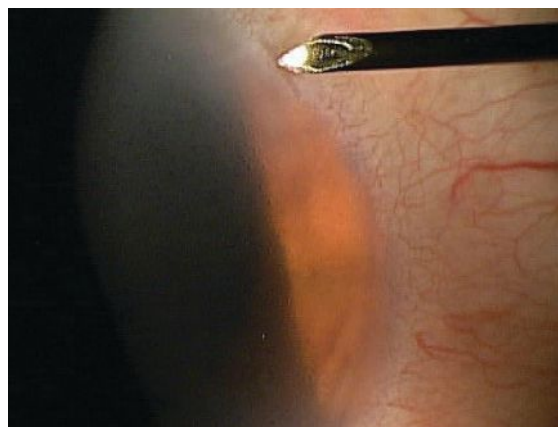


Photo: Howell Findley, OD

With a spud, place pressure on the conjunctival side of the paracentesis incision.

About Dr. Ajamian

Dr. Ajamian is board certified by the American Board of Optometry and serves as Center Director of Omni Eye Services of Atlanta. He is vice president of the Georgia State Board of Optometry and general CE chairman of SECO International. He has no financial interests to disclose.



EXPANDING EYECARE'S VIEW OF THE RETINA

Advanced imaging technology is giving eyecare providers a wider view of the retina to better monitor pathology

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EXPANDING EYECARE'S VIEW OF THE RETINA

Advanced imaging technology is giving eyecare providers a wider view of the retina to better monitor pathology



By John Warren, OD

Over the last several years, I have replaced or upgraded a number of imaging devices and instruments to improve patient care at my eyecare practice in Wisconsin. At Warren Eye Care, we are committed to evaluating patients in the most efficient manner possible. The latest technology makes it possible for us to rapidly collect data and information on the status of the eye so we can make an accurate and timely diagnosis.

Following the merger of iCare and CenterVue in 2019, iCare added the well-known and respected TrueColor Confocal Imaging Systems including EIDON, EIDON AF, EIDON FA, EIDON Ultra-Widefield (UWF) Module, DRSplus, and fundus automated perimetry with the COMPASS and MAIA. Since

I was already the satisfied owner of several devices from iCare—the DRSplus TrueColor confocal retinal imaging, the COMPASS automated perimeter with active retinal tracking, and the iCare tonometer—I recently decided to take my imaging and diagnostic capabilities to the next level with the EIDON Ultra-Widefield. I have not been disappointed.

The greatest benefit has been the ability to use one instrument for my entire fundus evaluation, improving clinic throughput. At the end of the day, I have fewer images to evaluate, leaving me with more time for patient care. The lack of dilation also is less intrusive and more comfortable for patients; after a minute or two they have no ongoing symptoms or issues, unlike the post-dilated fundus exam.



Case #1: Diabetic Retinopathy

For more than a decade, I have been caring for this 55-year-old white female with type I diabetes who developed background diabetic retinopathy about five years ago.

Using the flicker function on the COMPASS, the DRSplus, and more recently the EIDON Ultra-Widefield, I was able to observe a change in retinal appearance over time along with progression (which thankfully has been minimal to moderate). Along with the flicker function, the superior resolution of the EIDON UWF images allowed me to easily but, more importantly, clearly appreciate and judge the presence and progression of the retinopathy.

Combined with OCTA, I have an outstanding ability to not only evaluate the patient's retinopathy, but to follow its progression, and educate the patient and motivate her to improve her blood sugar control.

Figures 1 and 2. Image quality improvements can be seen between the earlier retinal image (top) and subsequent EIDON Ultra-Widefield (bottom) image. Images: John Warren, OD

NEXT-LEVEL IMAGING

The advantages of confocal imaging are many. In addition to offering superior image quality and capturing an unsurpassed depth of detail, this advanced technology reduces scattered and reflected light outside the focal plane; and

deftly captures ERM, drusen, dot blot hemes, etc. through cataract and media opacities.

There is no question that, compared to standard fundus imaging, TrueColor Confocal Imaging built into our COMPASS automated perimeter, DRSplus, and EIDON Ultra-Widefield

provides superior resolution, with much less impact from smaller pupils and media opacities. We've found that we get good images down to 1.8mm pupils.

Specifically, the EIDON Ultra-Widefield ability (up to 200° panoramic view) to illuminate early signs of ocular pathology in my patients means I can better evaluate the entire fundus than with traditional fundus exams (i.e., BIO, condensing lenses, and slit lamp evaluation). Even after 30 years of experience, I notice things in the peripheral retina that I couldn't see with my BIO.

Because I can spend more time examining the fundus structures vs. just having a fleeting glance at them with BIO, I'm much more likely to pick up on subtle findings, especially with the resolution provided by the EIDON Ultra-Widefield. Having a holistic view of the fundus helps greatly, not to

mention the comprehensive imaging records I have access to going forward. Certainly, there have been times I've felt the need to perform a DFE after UWF imaging, but in most cases, we are able to acquire high-enough quality images with UWF imaging alone to satisfy my clinical exam needs.

Another feature that is available on all iCare imaging devices is the "flicker" function. This enables side-by-side image comparison which has improved my ability to detect subtle changes and analyze especially challenging cases. I had no idea how dramatically it would improve my diagnostic process and efficiency until I had the COMPASS fundus perimeter for about six months. By then, not only did I have reliable visual field results, but I had imaged enough AMD and glaucoma patients to appreciate the power of easily flipping between current and previous images. Seeing

Case #2: Retinal Tear & BRVO

This 62-year-old white female patient has had hypertensive retinopathy and an inferior branch BRVO in her left eye that has waxed and waned with retinal edema and hemorrhage for about a decade. In January, the patient presented with a visual distortion in her left eye.

As was evident from the initial DRSplus image, the pre-retinal heme cleared over time, leaving a moderate ERM with significant pucker behind. Regression can be seen on the follow-up DRSplus image.

Subsequent EIDON Ultra-Widefield imaging revealed the ERM quite clearly, as well as a new horseshoe tear superior temporal. The ERM and the tear did not show up nearly as well on other retinal imaging devices I used.

The patient was sent to her retina specialist (with whom I have been sharing care over the last few years) for retinopexy. I have not seen the patient back for follow-up post-treatment, but I'm looking forward to seeing the specialist's work based on the EIDON Ultra-Widefield findings.

Figures 1, 2, and 3. In initial DRSplus (top) image, I observed the pre-retinal heme clear over time, leaving a moderate ERM with significant pucker. Follow-up DRSplus (middle) image revealed regression. Subsequent EIDON Ultra-Widefield (bottom) image showed the ERM quite well, as well as a new horseshoe tear superior temporal. Images: John Warren, OD



EXPANDING EYECARE'S VIEW OF THE RETINA

Advanced imaging technology is giving eyecare providers a wider view of the retina to better monitor pathology

drusen appear, watching ONH rim erode, and tracking the increasing/decreasing size of a diabetic heme are all powerful ways I can evaluate structures over time. Now I can't imagine practicing without this capability.

ADVANCING THE PRACTICE

All of the iCare technologies I've added have improved clinical efficiency and/or patient experience. Here are just a few examples:

- The EIDON Ultra-Widefield eliminates dilation time and enables patients to resume CL wear immediately after their exams.
- iCare rebound tonometry is more patient friendly than NCT and Goldmann, and much quicker to perform.
- Using the built-in review software enables us to create and review patient findings from any computer in the office.
- Because of automation and easy to navigate software, all of my iCare devices have been incredibly simple to

install and train staff on. My team unboxed, set up, and took our first images of my fundus with our new DRSplus in less than 15 minutes.

- Technology updates are rapid and seamless with iCare imaging devices. After we make a few selections on the devices, the iCare support team logs in and completes the process.

Patients have come to expect an exceptional experience in my office, thanks to the help of such technology advancements. Four out of 5 of our new patients comment on the ease of having pressures taken with the iCare tonometer, and they have responded positively to faster, more comfortable fundus evaluations. There is no doubt in my mind that iCare has helped us meet and exceed our patients' expectations. ■

John Warren, OD, is owner of Warren Eye Care, based in Mt Pleasant, Wis.

Case #3: Macular Degeneration

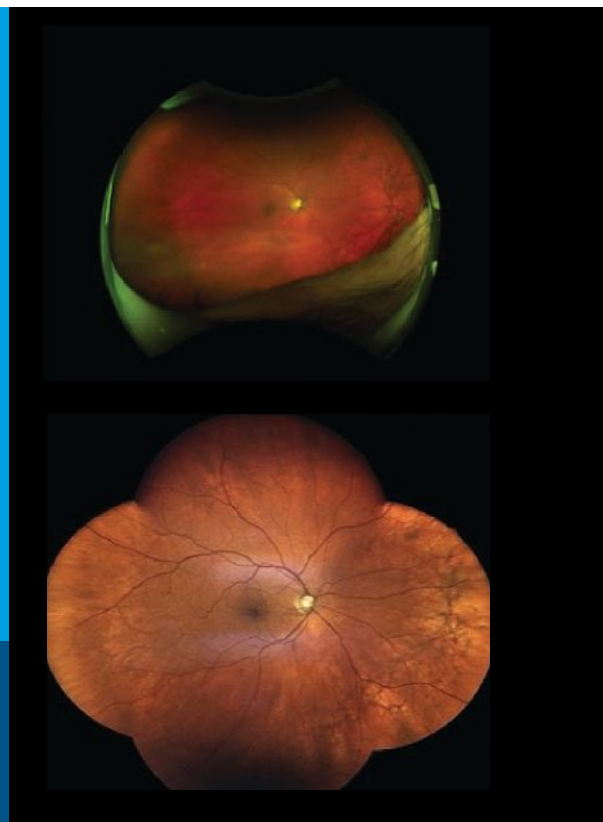
One of the most common finding I follow with my iCare imaging products is AMD. I utilize the TrueColor confocal imaging systems, red-free imaging to evaluate drusen, and the flicker function to monitor progression over time.

For the last decade, I have been following this 68-year-old white male who has had dry AMD for more than 20 years. As of now, he's not showing any SRNV.

The flicker function on the COMPASS and DRSplus has been extremely helpful for evaluating the patient's current status and any disease progression between patient visits.

Comparing the most recent EIDON Ultra-Widefield image to an earlier image, it becomes clear that TrueColor image quality and resolution are necessary to adequately evaluate and document this patient's macular findings.


Figures 1 and 2. When comparing the earlier (top) image with the more recent EIDON Ultra-Widefield (bottom) image it becomes clear that TrueColor confocal imaging quality and resolution are necessary to adequately evaluate and document this patient's macular findings. Images: John Warren, OD



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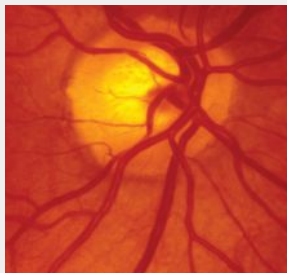
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EVALUATING VISUAL QUALITY IN AMD

Understand how to best serve your patients with this condition to help improve their quality of life.



BY REBEKAH LIN, OD
NEW YORK CITY

Age-related macular degeneration (AMD) is a retinal disease that affects millions of people globally. An estimated 288 million people are predicted to have AMD by 2040.¹ With a worldwide prevalence of 8.7%, it is one of the leading causes of irreversible blindness and vision impairment.

AMD primarily affects people later in life, and patients 55 and older should be screened for the condition through a dilated fundus evaluation and risk assessment profile.² Risk factors for developing AMD include a positive family history especially in first-degree relatives, cigarette smoking and Caucasian race. Additionally, factors such as female sex, increased exposure to sunlight, cardiovascular disease, diet and light-colored irises may be potential risk factors.¹⁻⁴

In AMD, there is characteristic drusen formation and pigmentary alteration in the macular region. Patients must have at least one druse that is intermediate in size (greater

than 63 μ m and less than 125 μ m) to be diagnosed with early AMD.^{4,5} As the condition progresses, there is loss of the photoreceptor layer and disruption of the retinal pigment epithelium (RPE), which may be due to oxidative damage, leading to geographic atrophy (GA).^{2,3} This is the dry form of late or advanced AMD. In some cases, there is growth of new and abnormal blood vessels stimulated by vascular endothelial growth factor (VEGF).⁴ This is known as wet or neovascular AMD.

Dry vs. Wet

Approximately 90% of patients with AMD have the dry form.⁴ For treatment of dry AMD, the Age-Related Eye Disease Study (AREDS) showed that a formulation of high-dose vitamins C and E, beta carotene and zinc helped reduce the risk of progression to advanced stages, defined as either the development of choroidal neovascularization or central GA. The use of AREDS vitamins was shown to be beneficial for those with either extensive intermediate drusen, one or more large drusen, noncentral GA in one or both eyes or advanced AMD in one eye.²

AREDS2, a follow-up study looking at the benefits of changing the treatment formulation, found no benefit from the addition of omega-3 fatty acids, lutein or zeaxanthin. However, the study suggested that in patients with a history of smoking, there is a potential increased risk of lung cancer when using formulations that include beta carotene. The AREDS2 study concluded that lutein and zeaxanthin could be used as substitutes.⁵

Other management strategies include intake of leafy green vegetables, protection against UV exposure and discontinuation of smoking.⁴ Additionally, studies are looking to see if medications, such as the complement inhibitor eculizumab, or gene therapy can be employed to treat GA.⁶

While less common than the dry form, wet AMD is responsible for 90% of cases with severe vision loss, which is defined as loss of six or more lines of distance acuity.⁷ Medical treatment options are currently only available for wet AMD and include laser photocoagulation, photodynamic therapy (PDT) and anti-VEGF injections.^{2,7,8} Laser photocoagulation targets melanin in the RPE to destroy

About the author

Dr. Lin is a graduate of the University of California Berkeley School of Optometry. She completed a residency in low vision rehabilitation at SUNY College of Optometry, where she currently works as an assistant clinical professor. She has no financial interests to disclose.



Fig. 1. The ETDRS chart can be placed at 4m, 2m or 1m.

neovascularization. However, it leaves behind an absolute scotoma due to the damage to the overlying retina and RPE and is becoming less commonly used in the treatment of exudative AMD.⁸ PDT was developed to minimize this damage and selectively target the neovascularization. It has been shown to prevent loss in approximately two-thirds of treated patients, though moderate vision loss still occurs despite treatment.⁷ Anti-VEGF intravitreal injections such as bevacizumab, ranibizumab or aflibercept can be administered to control neovascularization and regress vessel growth, with current studies looking at best follow-up practices and combination therapies for this first-line treatment.^{4,9}

As many patients go on to develop some form of vision loss, even in the presence or as a side effect of treatment, it is important to understand how this vision loss may present clinically. With both forms of AMD, there can be a reduction in best-corrected visual acuity (BCVA), loss of contrast sensitivity, development of central and paracentral scotomas, decrease in stereopsis and delay in dark adaptation. Patients also develop an inability to perform activities of daily living (ADL). They may present with a

multitude of complaints such as poor vision, difficulty driving, reading, recognizing faces and glare sensitivity. These patients should be evaluated by eyecare providers to determine if tools and strategies beyond traditional glasses and contact lenses can be used to improve visual function and quality of life (QoL).

Visual Acuity Changes

This may be noticed initially by the patient as they start experiencing difficulty seeing fine print and details. They may report things like blurry vision at all distances and difficulty reading street signs, menus and medication labels. In patients with AMD, visual acuity is what determines legal blindness, defined as BCVA of 20/200 or worse in the better-seeing eye or a visual field of no more than 20° in its widest meridian in the eye with the larger field.¹⁰ The visual field qualification is unlikely in patients with macular degeneration alone, as the peripheral visual field is spared. However, if patients have other conditions that affect the peripheral field such as glaucoma, they may qualify in that manner.

Resolution visual acuity can be measured using traditional vision charts such as the Snellen chart and the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, with the type of chart (*e.g.*, paper, projector, digital, etc.) affecting a patient's results (*Figure 1*). While the Snellen chart is widely used in the clinical setting, there are several flaws to its design that affect measurement of visual acuity in patients with visual impairment. For instance, there is only one line (20/200) between 20/100 and 20/400, which makes measuring acuity at these levels difficult.⁶

Patients with visual impairment typically perform better with less variable results using an ETDRS chart, especially in cases of advanced disease with vision worse than 20/200. The ETDRS chart allows for accurate measurement of low levels of acuity because it has more lines and

the working distance can be adjusted from 4m in cases of even poorer acuity to 2m or even 1m. The consistency of the type on the chart also makes it easier to read. Additionally, the ETDRS chart is used exclusively in clinical studies while case reports tend to be published using Snellen notation.¹¹

While measuring visual acuity is a key part of the examination, this component alone does not paint a complete picture of the visual function, or loss thereof, in patients with AMD. Visual acuity on high-contrast vision charts may remain intact while other aspects of visual function such as contrast sensitivity degrade over time. In addition, reading isolated optotypes one by one on a visual acuity chart may still be achievable while advancing GA continues to snuff out vision and create larger paracentral scotomas.

Contrast Sensitivity Concerns

This plays a large role in many ADLs and can be more indicative of functional difficulties than changes in acuity.^{12,13} Patients with AMD require higher luminance and contrast for letter recognition, which affects



Fig. 2. A Mars contrast set comes with three cards, available in both letters and numbers.



Fig. 3. A monocular handheld telescope (left) and a binocular telescope in a frame.

general visual function. They may report difficulty seeing in low-light environments, such as in subway stations and restaurants or in poor weather conditions. They may also have increased sensitivity to glare and difficulty reading low-contrast media such as newspapers. Words like “foggy” or “hazy” are commonly used to describe their vision. Additionally, contrast sensitivity affects a patient’s reading ability, with reduced contrast leading to reduced reading ability and speed.¹³

Clinically, there are many ways to determine contrast sensitivity. It is commonly measured with either a Mars or Pelli-Robson chart based on the patient’s acuity level (*Figure 2*). The Mars chart has been shown to produce reliable and repeatable results in patients with BCVA of 20/250. It is smaller than the Pelli-Robson and is printed on a hard material as opposed to cardboard, making it a more convenient, portable and accessible tool in clinical settings.¹⁴ Digital visual acuity charts can often measure contrast in addition to standard high-contrast acuity, though the functionality differs depending on the system.

Contrast loss is categorized as moderate, severe or profound and can be confounded by other factors such as cataracts and dry eye, which are

often comorbidities in these patients. Contrast testing should be considered in all patients with AMD as an additional method of monitoring change and visual impact of the condition.

Central Scotomas

Many patients with AMD develop central scotomas due to macular atrophy or as a side effect of laser photocoagulation, both of which affect visual acuity and contrast sensitivity negatively. Scotomas due to pathology may also continue to change as the condition progresses. Patients may complain of difficulty keeping their place while reading and recognizing faces. They may report areas of distortion or objects that “appear out of nowhere” rather than dark spots in their vision.¹⁵

Traditional visual field testing is difficult for patients with poor fixation, such as in AMD, but microperimetry, also referred to as fundus perimetry, can be used to map these central scotomas and track their progression over time. Microperimetry uses tracking software to account for the location and stability of fixation, which allows for more accurate and real-time documentation of retinal sensitivity than traditional methods. These results can also be overlaid on a fundus photograph.¹⁶ The Amsler

grid is another option that is widely accessible and doubles as an educational device and home monitoring aid for the patient to check for any changes in their vision between appointments.

In a healthy eye, the fovea has the highest density of cone photoreceptors, allowing for maximum visual acuity. However, because of central scotomas, patients with AMD may develop eccentric viewing, where they fixate using non-foveal points. As the peripheral retina is not as efficient in word recognition and processing, these patients experience reduced visual span and temporal processing.^{17,18} They have more difficulty reading and slower reading speeds than patients with reduced central acuity alone.^{15,17} Studies have shown that reading is the primary concern when patients with AMD seek further treatment, with over 85% reporting difficulty in this region.¹⁹

Patients with macular degeneration can also have poor stereopsis and difficulty with binocular function as they lose central vision due to the brain’s inability to fuse dissimilar images. While there are still monocular cues, disparate images seen by both eyes are required for depth perception. One study showed a loss of stereopsis due to reduced acuity and contrast sensitivity where age-matched patients with normal acuity and contrast sensitivity did not experience any loss.¹⁹ Another found that patients with AMD and stereopsis had higher overall functional visual abilities with better reading abilities, visual motor skills and mobility skills than those who did not. There was no correlation with BCVA between the two groups.²⁰

Loss of stereopsis can also present as difficulty with mobility, such as navigating curbs and steps and reaching for objects, and general clumsiness including knocking over glasses or spilling when pouring. It can affect a patient’s ability to drive, even if acuity and fields remain intact in one eye. There are many methods of measuring stereopsis during a clinical

exam, one example being traditional stereoacuity test booklets. Follow-up with questions regarding the patient's visual function for further evaluation and management.

Management and Rehabilitation

AMD can affect the visual system in many ways, and the impairment is usually permanent. A study performed on vision-related QoL showed the importance of high contrast acuity and contrast sensitivity and how vision loss secondary to AMD negatively affects both visual function and the socioemotional status of patients. Tasks such as reading, driving and facial recognition are all critical to vision-related QoL and drive patients to seek further services.^{19,21}

Additionally, vision-related QoL is directly related to the severity of vision loss.⁷ Rehabilitation is important to keep in mind in the comprehensive management of patients with AMD. Patients with even a small amount of visual impairment may find it difficult to perform ADLs and could benefit from low vision services. This also holds true when the impairment is only monocular. Early referral is critical, especially as the condition is progressive. Low vision rehabilitation refers not only to optical management but also to training, counseling and other interventions

through collaboration with rehabilitation specialists.

Low vision management of patients with AMD starts with an expanded functional history. Providers need to understand the patient's specific goals and use this information in conjunction with exam findings to offer the most appropriate recommendations. Factors to consider include working distance for the task, portability of the device and patient ability to physically manipulate the device. Management beyond traditional glasses and contact lenses includes the use of devices for distance and near, contrast enhancement and glare reduction. Non-optical aids, orientation and mobility training and traditional vision therapy techniques can also be employed. Management for patients with AMD should be personalized and aim to improve QoL and independence.

The exam should start with an accurate refraction to determine the patient's BCVA. One study found that 11% of new low vision patients showed improvement of two lines of acuity or more through refraction alone.²² A trial frame refraction rather than a traditional phoropter refraction is recommended for these patients to allow for eccentric viewing as needed. For near add determination, these patients may require a higher

add, which requires shortening of the working distance. This should be prescribed as a pair of separate reading glasses, as a high add in a multifocal lens can increase the risk for falls.

For further distance enhancement beyond refractive correction, telescopes may be used (*Figure 3*). Telescopes can be monocular or binocular, handheld or spectacle-mounted. They are used for spotting distant objects such as street signs, not for ambulation. Training is needed to teach patients proper techniques to best work the device. Spectacle-mounted telescopes may be prescribed for driving in some states with appropriate patient selection, training and rehabilitation.

For near enhancement, options include high-powered adds, handheld magnifiers, stand magnifiers and electronic magnification (*Figures 4 and 5*). While magnifiers can be purchased at many retailers and stores, patients should undergo an evaluation with an eyecare provider to find the magnifier that is best suited for their visual needs. Personal electronic devices such as smartphones or computers have built-in accessibility features, and additional applications and programs can be downloaded to magnify items on the screen. Cameras in smartphones and electronic magnifiers can also magnify objects in real



Fig. 4. An illuminated handheld magnifier (left), a dome magnifier—a type of stand magnifier (middle)—and a pair of prism half eye glasses.



Fig. 5. An example of a portable electronic magnifier displaying enhanced negative contrast.

Third, the scleral contact lens maintains the positioning of the light relative to the eye.

“In a traditional treatment, if you’re on the table underneath the lamp and you move out of position, the illumination is no longer aimed correctly,” he points out. “For keratoconus therapy, some small amount of patient movement can be tolerated, but for refractive correction, mistargeting could cause unacceptable errors. The lamp-based systems try to compensate for patient movement by putting trackers in the system that turn off the light if the patient moves. But when you put the light on a scleral contact lens that sits on the eye, if the eye moves, the device moves with it. It becomes an ambulatory procedure. In fact, our clinical procedures were done in the exam room chair.”

Dr. Chuck explains that the first human study was recently done to ensure that the form, fit and function of the device is ready for healthy eyes. Ten patients with advanced keratoconus were treated. “It was a challenge to get some of the later patient visits done, given pandemic shut-downs,” he notes. “However, we were able to complete the pilot trial, and it confirmed that the system works well, is safe, and treats keratoconus effectively, as expected. The data were published last year in *Translational Vision Science & Technology*.¹⁰ Now we’re in the planning stages for our initial refractive studies and the larger keratoconus trials for approval.”

Dr. Chuck says the company has been working on several additional modifications that might enhance the CXLens system in the future, including a proprietary riboflavin formula intended to increase penetration through the cornea, and a highly oxygenated wetting fluid. In the meantime, it turns out that the results using standard elements such as commercially available riboflavin have been very good.

“Having sufficient oxygen is im-



The CXLens performs cross-linking via a contact lens placed on the eye, which the company says increases patient comfort and eliminates the need for eye tracking.

portant to speed up a cross-linking treatment,” he says. “Hence, we came up with the idea of using a special highly oxygenated fluid as a wetting solution between the lens and the cornea. For the pilot trial, though, we used the commercially available solution and the results were good, so it’s possible we may not need to use the hyper-oxygenated fluid, or the proprietary riboflavin formula. Of course, we still plan to try them, to see if we can get even better results.”

For refractive indications, the on-eye UV delivery lens also incorporates a tiny ultrasound transducer that can provide real-time measurements of the changes in the cornea produced by the treatment. (For more on that, see *Refractive Correction*, below.)

Cross-linking Via an Eye Drop

Another non-traditional approach to corneal cross-linking generates the cross-linking pharmacologically using an eye drop, rather than surgically. The developer, iVeena Delivery Systems in Salt Lake City, says that data from a Phase I/IIa study has demonstrated that the IVMED-80 drop strengthens the cornea and causes flattening. The drops were recently licensed by Glaukos for further clinical trials and development.

The drop was created by cornea specialist Bala Ambati, MD, president of the Pacific Clear Vision

Institute in Eugene, Oregon, and a research professor at the University of Oregon. Dr. Ambati’s research revealed that lysyl oxidase, a natural enzyme in the cornea, mediates crosslinking. In fact, Dr. Ambati found a number of clinical studies that associated a deficiency of lysyl oxidase with keratoconus.¹¹⁻¹⁷ Copper is a key factor in lysyl oxidase activity, so the IVMED-80 drop was designed to raise the amount of copper in the cornea; that, in turn, increases lysyl oxidase activity in corneal cells. Animal studies found no accumulation of copper in the blood, liver or kidneys after use of the drops.

The Phase I/IIa study of IVMED-80 involved 33 patients with keratoconus; one-third of the patients received placebo; one-third received IVMED-80 for about six weeks, and another third received the drop for 16 weeks.¹⁸ Results included:

- The patients who received the drug for 16 weeks ended up with a 1-D flatter Kmax; those in the placebo group saw a progression of 0.46 D of Kmax during the same period.
- On average, there was no regression in the 16-week group after stopping the drop.
- The drops cause no inflammation, stinging or redness.

“Cross-linking can be induced by surgery and ultraviolet light, or by the presence of an enzyme that’s normally present in most patients but is deficient in keratoconus patients,” notes Dr. Ambati. “Our drop increases the presence of that enzyme, and mass spectrometry on rabbit eyes has demonstrated that this results in increased cross-linking. Either surgery or drops can be used to induce cross-linking, but the drops have obvious advantages over traditional cross-linking because there’s no corneal scraping or pain for the patient.”

Dr. Ambati points out that using a drop makes sense, at least in part because surgical treatments don’t

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Non-optical resources and management strategies should be considered as well, as there are many devices designed for patients with visual impairment to help them complete specific tasks that may otherwise be difficult. For example, patients with contrast loss may benefit from a bold-tipped pen for writing. When the service is available, they can request materials in large print, including medication labels, newspapers and novels. Tools such as liquid level indicators and large-print wristwatches are also options.

Mobility training by a specialist may be beneficial to acquire techniques for safe and independent navigation, as patients may experience difficulty ambulating with their reduced vision due to decreased acuity, contrast and stereopsis and the presence of scotomas. This training does not necessarily refer to a mobility cane or guide dog, as these tools are selected by rehabilitation therapists based on the patient's specific requirements.

Referral to occupational therapy may also be beneficial, as patients can work one-on-one with a therapist to enhance performance in areas such as reading, grooming, meal preparation, eccentric viewing techniques and low vision device use.²³

Even with appropriate magnification, patients with central scotomas still have difficulty reading.¹⁷ Traditional vision therapy techniques supplemented with home therapy activities can be used to improve visual performance in these patients by enhancing saccades and pursuits.^{18,24}

In addition to visual changes, there can be a profound psychosocial impact on patients as they experience progressive vision loss. Vision plays a significant role in the way we interact with the world, and loss thereof can be discouraging and isolating. Patients often express anger, frustration, sadness and distress that their eyes do not work as they once did. The Patient Health Questionnaire-2 can be used to screen for depres-

sion. These patients can benefit from services such as talk therapy, which is available in person, over the phone or through video conferencing, making it more accessible to everyone.²⁵

Patients with vision loss, especially central as in AMD, can experience visual phenomena such as photopsia or formed images that are not physically present. In the AREDS2 study, nearly 90% of participants reported this side effect at least once during the 10 years of follow-up.⁵ This occurrence, Charles Bonnet syndrome, can be an alarming experience for patients who are not properly educated on the condition. They should be reassured that these experiences are common and on their own, do not indicate neuropsychiatric disorders.²⁶ However, further workup may be needed to clarify the etiology, as visual phenomena can also be a side effect of medications or other conditions.

Takeaways

AMD is a condition that affects a substantial number of patients globally and causes multiple functional vision problems. There is a combination of both modifiable and nonmodifiable risk factors, and treatment is only available for certain forms of the disease. Many of these patients experience some form of vision loss and must be monitored carefully and made aware of resources such as low vision rehabilitation. Candidates should be referred for these services at an early stage and given tools to help them continue performing ADLs independently. ■

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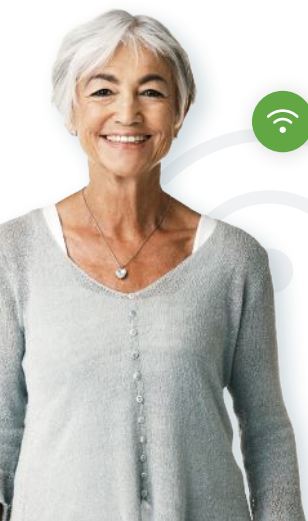
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A GUIDE TO DEMYELINATING DISEASES OF THE CNS

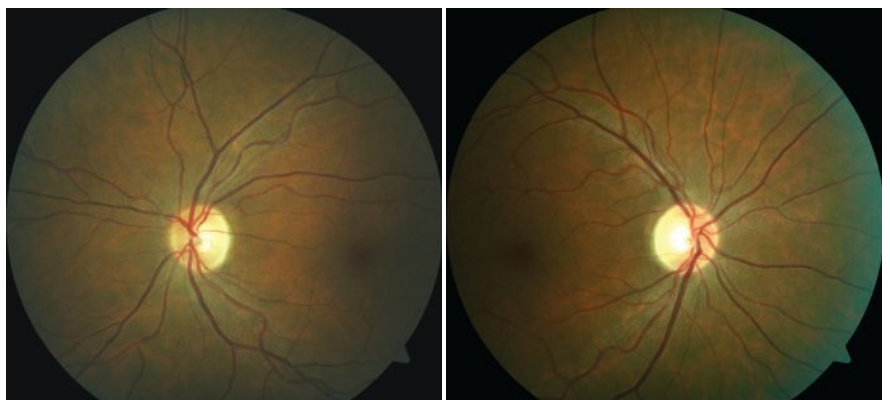
This overview can help you better understand the clinical features and findings of optic neuritis, neuromyelitis optica and MOG.



BY MICHAEL DELGIODICE, OD
RAMSEY, NJ

Demyelinating disorders represent a heterogeneous group of central nervous system (CNS) pathologies characterized by the loss of myelin sheath or the cells that form them. Primary demyelination of the CNS represents a category within a broad spectrum of inflammatory autoimmune disorders that occurs against the backdrop of chronic inflammation and neurodegeneration. Multiple sclerosis (MS) remains the most common primary CNS demyelinating disorder, affecting white and grey matter of the brain, spinal cord and optic nerve.¹ Until recently, neuromyelitis optica (NMO) spectrum disorder and myelin oligodendrocyte glycoprotein (MOG) antibody disease represented variants of the disease despite their distinct pathologic and phenotypic expressions.

The advent of antibody testing for NMO spectrum disorder (AQP4-IgG) and MOG antibody disease (anti-MOG) has enabled clinicians to better differentiate among each disease and more accurately determine the prognosis and response to therapy.



Asymptomatic bi-temporal optic disc pallor representing progressive demyelination of the optic nerve without a history of optic neuritis.

Optic neuritis (ON) is a general term that is used to describe inflammation of the optic nerve that can occur in isolation or as a manifestation of a systemic disease process. Numerous etiologies are responsible for ON and broadly classified as typical or atypical based on clinical, laboratory and imaging findings. The aim of this article is to compare and contrast the immunopathology, clinical presentation, diagnostic criteria, and management of MS, NMO spectrum disorder and MOG antibody disease in the setting of typical and atypical ON. Additionally, systemic causes of atypical ON will be reviewed.

Typical Optic Neuritis

This classification describes an underlying demyelinating process that occurs in isolation or as a clinical manifestation of MS. Performing comprehensive ophthalmologic clinical examination, including neuroimaging and studies and laboratory evaluation, is necessary to differentiate the three primary demyelinating diseases.

In cases of ON with two or more non-contrast enhancing lesions on magnetic resonance imaging (MRI), a diagnosis of clinically isolated syndrome can be made, which is associated with a high risk of developing MS.

About the authors

Dr. DelGiodice previously practiced at Associated Eye Physicians in Clifton, NJ, and recently accepted a position as a medical science liaison for Sun Pharmaceuticals. His industry role had no bearing on the content of this article. Dr. DelGiodice is also a Fellow of the American Academy of Optometry.

Suspected cases of acute demyelinating ON should undergo a comprehensive ophthalmologic examination and ancillary testing (Table 1).²

Acute demyelinating ON is the presenting sign of MS in about 20% of patients, and will occur over the course of the disease in another 50%.³ In the general population, the annual incidence of new-onset acute demyelinating optic neuritis has been reported to be 0.5 to 5.1 per 100,000.⁴ The disease typically affects Caucasians with a female predominance of two to one.²

The most common presentation of typical acute demyelinating ON includes acute unilateral loss of vision accompanied by pain on eye movement, diffuse and central scotoma, and dyschromatopsia.⁵ Additional complaints include recurring photopsia, exercise or heat-induced vision loss (*i.e.*, Uhthoff phenomenon) and anomalous perception to moving objects (*i.e.*, Pulfrich effect), the latter of which develops as vision improves.⁵

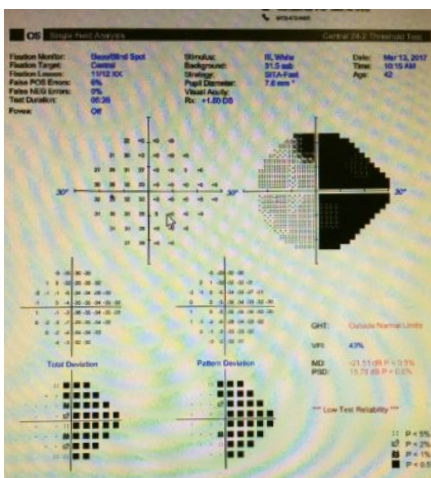
The degree of vision loss can range from normal visual acuity to no light perception with a decrease in contrast sensitivity. Pain and eye movement that precedes acute central vision loss with a normal or mildly edematous optic disc edema is the most common clinical features observed in MS-related optic neuritis. When present, these key clinical features can be pathognomonic for a demyelinating event.

Following an acute episode of typical acute demyelinating ON, patients will experience near normal improvement in visual acuity, visual field and color vision, with the exception for contrast perception. Typically, the loss of acuity is described as taking place over hours to days with gradual improvement over days to weeks.⁶ Visual field defects are commonly observed with diffuse central scotomas occurring most frequently.⁷ Swelling and hyperemia of the optic disc (*i.e.*, papillitis) is observed in only one-third of cases, while the remaining two-thirds appear normal (*i.e.*, retrobulbar ON).³

Neuroimaging is required to determine the visual and neurologic

TABLE 1. CLINICAL EVALUATION OF SUSPECTED ON²

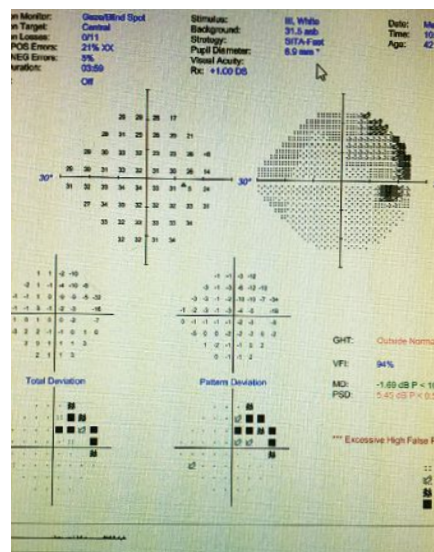
General Examination	Special Testing
Best-corrected visual acuity	MRI of the brain and orbits with and without contrast
Automated VF testing	NMO-IgG
Color vision testing with particular attention to red desaturation	Anti-MOG
Pupillary examination evaluating for an afferent defect	
Optic nerve examination with high-resolution	
Optical coherence tomography of the retinal nerve fiber layer	



Partial non-congruous right hemianopia in a patient with relapsing-remitting MS.

prognosis, and to differentiate among alternative demyelinating diseases. In contrast to acute typical ON, optic nerve pallor is a finding that suggests longstanding, chronic demyelination secondary to MS. In the absence of key features that suggest an isolated demyelinating event or MS-related ON, there is a greater likelihood that the patient has atypical ON.

MRI of the brain with and without contrast is the most important test ordered to determine systemic demyelination as well as to understand the visual and neurological prognosis. Ideally, it is recommended to include contrast-enhanced imaging of the orbits, in order to assess the level of activity, and to discount masquerading diseases such as orbital tumors (*e.g.*, meningioma) and lymphoproliferative lesions (*e.g.*, leukemia and lymphoma). In the setting of acute demyelinat-



ing ON, contrast enhancement of the optic nerve on MRI has been observed in 94% of patients and has distinguishing features that differentiate it from NMO spectrum disorder and MOG antibody disease (Table 2).⁸

While there is no one single biomarker that can confirm the presence of MS, the revised McDonald criteria provides supportive data that is used to establish the diagnosis and assess the response to therapy (Table 3).⁹ In the setting of typical ON, abnormal neuroimaging increases the probability of developing MS at 15 years from 25% to 72%. On the basis of the Optic Neuritis Treatment Trial (ONTT), the five and 10-year risk for developing recurrent ON are 28% and 35%, respectively, occurring more frequently in patients with MS.⁵

Ancillary testing (*e.g.*, cerebrospinal fluid (CSF) analysis and blood work)

TABLE 2. MRI FINDINGS IN PRIMARY DEMYELINATING DISORDERS⁸

Etiology	MRI Finding
Isolated ON	Orbit: hyperintense signal on short T1-inversion recovery images and intense post-contrast enhancement
MS	Brain: Dawson's fingers Spinal cord: plaques of the short segment <two-thirds the circumference
NMO spectrum disorder	Brain: peripendymal lesions surrounding third ventricle, cerebral aqueduct, thalamus, hypothalamus and midbrain Spinal cord: plaques of long segment >four vertebral bodies
MOG antibody disease	Orbit: long segments of optic nerve enhancement with extension to the peribulbar fat

are not considered standard procedures when the clinical findings are consistent with MS-related ON. Analyzing the CSF has value when MRI findings are not definitive and when the clinical findings are not consistent with MS. Laboratory testing is also not an international standard and is reserved for cases that suggest an alternative etiology. In a large cohort of patients, testing for antinuclear antibodies, syphilis serologies and chest X-ray were found to have no clinical indigence.⁵

Following a diagnosis of MS-related ON, treatment for MS is aimed at treating the acute attack and reducing the frequency of attacks. For acute attacks, intravitreal (IV) methylprednisolone is the standard treatment.⁵ It has been well-established that three to five days of treatment with IV methylprednisolone leads to faster improvement in visual recovery but has no effect on the finale outcome in vision.⁸ Following guidelines from the ONTT, IV methylprednisolone followed by oral prednisone resulted in lower rates of MS within the first two years.⁵ Plasma exchange can be used if the attacks are severe and the disease is recalcitrant to corticosteroids.⁸ Long-term immunosuppression is recommended to reduce morbidity and mortality. Treatment options for relapsing and remitting MS include injectable, oral and IV infusion.⁹

Fingolimod became the first drug indicated for treating relapsing MS; it is a once-daily oral medication that works by blocking lymphocytes from escaping the lymph and traveling into

the CNS. Siponimod is also an oral medication taken daily and the first that is indicated for to treat secondary progressive disease by inhibiting both T and B cells. Ocrelizumab is approved for all forms of MS (e.g., relapsing-remitting, primary progressive and secondary progressive). It is given in an IV infusion every six weeks and works by destroying B cells. Ofatumumab is an injection given once a month. It too targets B cells and is approved for relapsing MS.

It is important to understand both the form of the disease as well as the medication in order better assess the visual status and confidently address patient concerns. The short-term goal in disease-modifying agents is to decrease the amount of lesion activity as detected on MRI. After initiating therapy, the goal of the neurologist is to monitor for progression and identify early signs of toxicity.⁸

Multiple Sclerosis

Primary demyelinating disorders are chronic inflammatory disorders of the CNS characterized by cell-mediated autoimmunity and neurodegeneration of brain, spinal cord and optic nerve.¹¹ Despite the elusive nature of its pathogenesis, there are several factors that have been implicated in MS: infection (e.g., Epstein-Barr virus and human herpes virus-6), low vitamin D, geographic gradient, obesity, smoking and genetic factors.¹² With over 200 identified genetic inheritance patterns, HLA-DRB1 represents the most common variant.¹³



Demyelinating plaques within the cerebral hemispheres



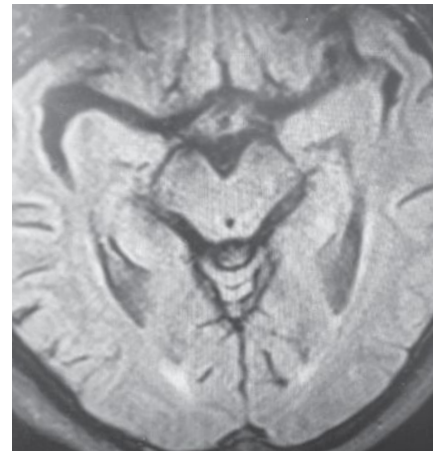
Normal fluorescein angiography of the right eye in a patient with acute vision loss attributed to acute ON.

The annual incidence of MS is 2.1 cases per 100,000 with a prevalence rate of 35.9 per 100,000 worldwide.¹³ Women are affected more than men with a predominance of two to one, and highest among populations that are more distant to the equator.¹² In the CNS, myelin sheaths are formed and maintained by oligodendrocytes. Both the adaptive and innate immune system are responsible for stripping the myelin lamellae and removing myelin fragments.

Demyelination represents the final common pathway of MS. While acute demyelinating lesions can occur anywhere in the CNS, there is a predilection for areas with high venous density as inflammatory cells egress through veins from blood to brain (e.g., Dawson fingers).^{14,15} Contrary to acute lesions, smoldering demyelinating lesions are often associated with progressive MS.¹⁵

TABLE 3. SUMMARY OF THE 2017 REVISED MCDONALD CRITERIA⁹

Clinical presentation	Additional findings needed for MS diagnosis
≥ Two clinical attacks and objective clinical evidence of ≥ two lesions	None; however, magnetic resonance imaging (MRI) is typically obtained to both exclude other diagnoses and stage the severity of disease.
≥ Two clinical attacks and objective clinical evidence of one lesion	Dissemination in space: an additional clinical attack implicating a different central nervous system site or by MRI.
One clinical attack and objective clinical evidence of ≥ two lesions	Dissemination in time: an additional clinical attack or by MRI; or cerebrospinal fluid-specific oligoclonal bands.
One clinical attack and objective clinical evidence of one lesion (<i>MS at first episode if initial MRI criteria are met for dissemination in space and in time or dissemination in space plus cerebrospinal fluid-specific oligoclonal bands</i>)	Dissemination in space: an additional clinical attack implicating a different CNS site or by MRI. Dissemination in time: an additional clinical attack or by MRI or cerebrospinal fluid-specific oligoclonal bands.



Multifocal white matter lesions in a patient with relapsing and remitting MS.

These lesions are characterized by loss of peripheral axons that are replaced with iron-containing microglia, hypothesized as a CNS-resident immune response.^{15,16} Lastly, chronic lesions are characterized by circulating T cells and macrophages surrounding an area that is hypocellular.^{16,17} Treatment for primary MS is similar to MS-related ON discussed previously.

NMO Spectrum Disorder

First described in the late 19th century as simultaneous acute demyelinating ON and myelitis, NMO is now considered just one of a number of phenotypes that represent NMO spectrum disorder, particularly reflected by prominent perivascular immunoglobulin deposition and complement activation with autoantibodies to aquaporin-4 (AQP4).^{18,19} Patients with signs and symptoms of NMO spectrum disorder require serum antibody testing via cell-based assay of AQP4-IgG plus contrast-MRI of the brain, orbits and spinal cord.⁹

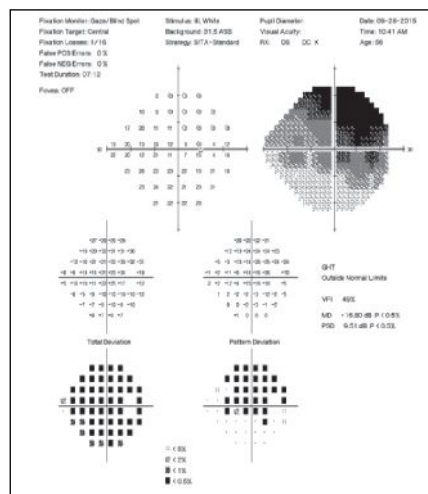
The mean time from the first symptom to relapse is 8.5 months regardless of AQP4-IgG status. However, the presence of AQP-4 antibodies increases the likelihood of severe visual impairment, recurrence of ON, and subsequent development of transverse myelitis; longitudinally extensive transverse myelitis describes inflammation involving a minimum of three contiguous vertebral segments.^{9,20}

TABLE 4. CLINICAL AND PARACLINICAL FINDINGS OF MS, NMO AND MOG ANTIBODY DISEASE³²

Characteristics	MS	NMO Spectrum Disorder	MOG Antibody Disease
Age	~30	~40	Early to mid-30s
Sex	More common in women	AQP-4 -NMO: equal distribution AQP-4 +NMO: more common in women	Slight predominance in women
Clinical findings	ON, typically good recovery	ON, severe and limited recovery	ON, better VF recovery compared with AQP-4+ ON
Disease course	Relapsing or progressive	Relapsing	Monophasic or relapsing
Types of relapse	Brain, spinal cord or optic nerve	ON and longitudinally extensive transverse myelitis	ON- commonly (more than NMO spectrum disorder)
MRI brain	Always abnormal, presence of Dawson's fingers, sub-cortical lesions	Abnormal T2 signal in 60% around third and fourth ventricles	Abnormal in 45% to 72%, small, fluffy T2 hyperintense lesions



Optic nerve pallor of the left eye following resolution of retrobulbar ON.



Incomplete superior visual field scotoma involving fixation.

NMO spectrum disorders affect women more than men. Unlike MS, these disorders are often found in non-Caucasians with a significantly lower incidence and prevalence rate of 0.053 to 0.40 per 100,000 and 0.52 to 4.4 per 100,000, respectively.^{20,21} Core clinical features of NMOSD include acute demyelinating ON, myelitis, area postrema and other brainstem syndromes, as well as diencephalic and cerebral sign.²² Systemic symptoms include intractable nausea and vomiting, hearing loss, diplopia, vertigo, facial palsy and sleep disturbances.²²

Aside from acute demyelinating ON and myelitis, the diagnostic criteria for NMO spectrum disorder has expanded to include a larger topographic area of CNS involvement and seropositive AQP-4-IgG.²³ Clinically, the diagnosis of NMO spectrum disorder is most accurately characterized as NMO spectrum disorder with AQP4-IgG or without AQP4-IgG.^{23,24} Traditionally, acute attacks are treated with IV methylprednisolone and plasma exchange; however, up to 50% of patients experience a recurrence in symptoms.²⁴ Additional broad-spectrum immunosuppressive agents have also been used but with lower efficacy as compared to newer targeted therapies.

There have been three recently approved monoclonal antibody medications: rituximab for B cell inhibition;

eculizumab, a complement inhibitor; inebilizumab, an anti-CD9 agent; and satralizumab, an anti-leukin 6 receptor. All therapeutic agents target specific disease pathways in patients with AQP-4 antibodies and have been shown to be safe and effective for long-term immunotherapy, as traditional MS medications may increase the rate of relapse.²⁴ Specifically, satralizumab is effective for AQP-4 seronegative NMO spectrum disorder, and in patients with AQP-4 seropositive disease, eculizumab was found to have a 94% reduction in the rate of relapse.

Acute Disseminated Encephalomyelitis (ADEM) and MOG Antibody Disease

ADEM is a monophasic demyelinating disorder of the CNS, most prevalent in children, characterized by extensive macrophage involvement.²⁵ CNS involvement usually shows small, non-confluent, demyelinating lesions within the perivascular region. This distinguishing factor differentiates it from large confluent perivenous lesions observed in MS.²⁵ Demyelinating lesions in ADEM can occur throughout the CNS, including the white matter, cortex, thalamus and basal ganglia. ADEM typically affects children and young adults following seasonal changes, infection or vaccination (*e.g.*, Epstein-Barr, human herpes virus-6 and coronavirus).²⁶

MOG is a minor myelin protein that is expressed on the surface of myelin sheaths of the CNS and is targeted by IgG1 antibodies.²⁷ Lesions are typically characterized as large, hazy, bilateral and with vast topographic involvement, including longitudinally extensive transverse myelitis.²⁷ Similar to NMO spectrum disorder, this form of myelitis usually has greater proclivity for the thoracic cord.²⁷

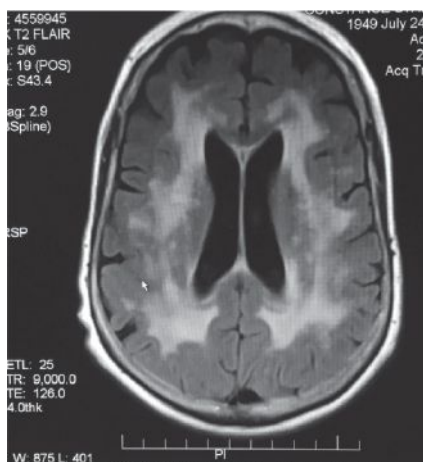
In children, up to 60% with MOG antibody disorder have bilateral thalamic involvement and lesions within the cerebellar peduncle.²⁸ Just over half of these patients have short hyperintense lesions within the thoracic cord.²⁸ CSF analysis has been shown to

express pleocytosis, elevated protein, and limited oligoclonal bands. Cell based serum assays are recommended for detecting MOG-IgG when clinical features are consistent with a diagnosis of MOG antibody disease.²⁸

Bilateral, simultaneous acute demyelinating ON is the most common initial presenting sign, reported to occur in 51% of MOG antibody disease-related ON patients.²⁹ Pain on eye movement and papillitis are two of the most common clinical features. While loss of vision is typically severe in the acute stage, less than half of patients present with normal brain MRI.³⁰ In contrast, MOG antibody disease testing has been shown to be highly specific and sensitive during an acute attack.²⁹ This highlights the importance of both early detection and timely serologies. As compared with both NMO spectrum disorder-related ON and MS-related ON, clinical and paraclinical findings in MOG antibody disease show both similarities and differences (*Table 4*).²⁹

Timely diagnosis helps to establish the prognosis and choose the most appropriate treatment, which is to eliminate systemic MOG antibodies and improve the visual outcome. Typically, treatment consists of IV methylprednisolone based on weight. In cases where there is a weak response to IV methylprednisolone or recurrence, either intravenous immunoglobulin or plasma exchange are additional options. The symptoms of recurrent MOG antibody disease-related ON can also be dampened using disease modifying agents. Because poor visual acuity has been reported in 16% of patients, timely and judicious management is necessary to preserve visual function and quality of life.³¹

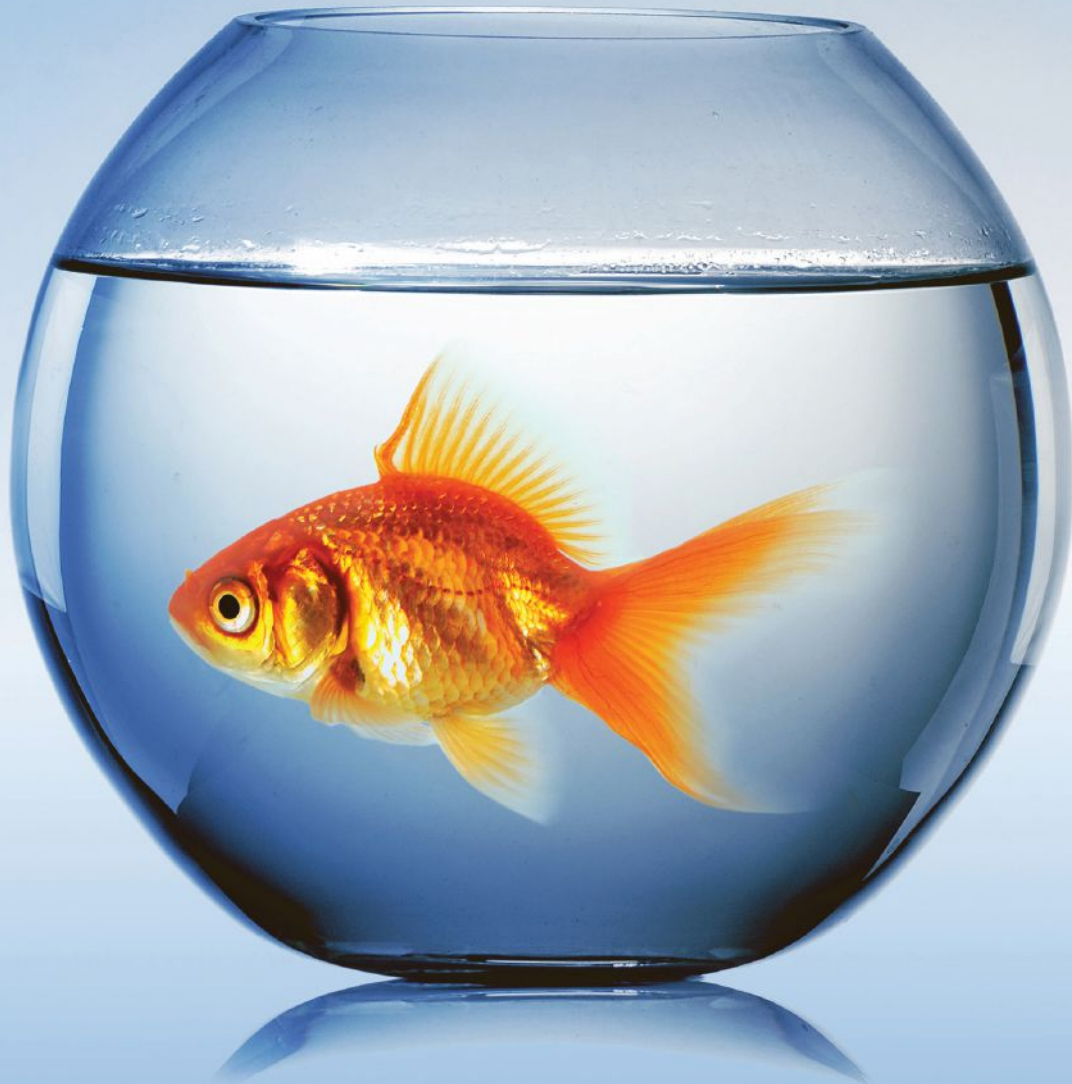
Acute treatment for MOG antibody disease is IV methylprednisolone and plasma exchange. Disease modifying agents used for long-term therapy include IV immunoglobulin, rituximab, mycophenolate mofetil, methotrexate and azathioprine. The role of steroids as adjunct treatment with immunosuppressants still remains unanswered.²⁸



Axial MRI T2 FLAIR showing confluent white matter lesions representing demyelination from leukoencephalopathy.

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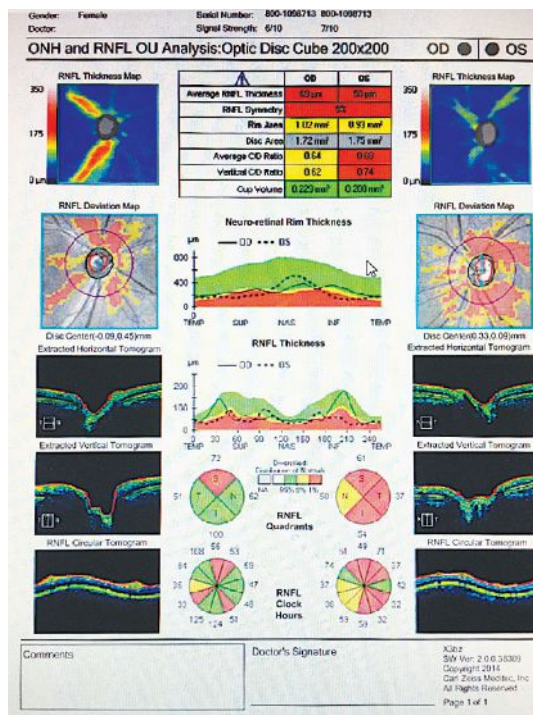
Takeaways

Knowing which clinical features are atypical for ON (e.g., bilateral, poor visual recovery) and which are consistent with MS, NMO spectrum disorder and MOG antibody disease is important for preserving vision and quality of life.

A patient who is suspected of optic neuritis needs comprehensive eye examination, including ancillary testing (i.e., OCT, fundus photography and automated perimetry). In the absence of systemic disease and atypical findings, the patient needs emergent contrast-enhanced MRI of the brain and orbits with and without contrast and fat suppression. Findings that are consistent with MS-related ON should receive IV methylprednisolone followed oral corticosteroids in order to speed visual recovery and reduce the risk of developing MS. Additional therapy is recommended for long-term immunosuppressive therapy. The optometrist should perform serial visual fields, OCT and fundus photography. Comanagement with a neurologist who subspecializes in MS is recommended.

In the presence of a history of systemic disease (e.g., autoimmune disorders or infection), abnormal neuroimaging or ophthalmologic findings consistent with atypical ON, the patient requires additional contrast-enhanced neuroimaging of the spine along with laboratory tests and possible CSF analysis. It is especially important to differentiate among the three primary demyelinating diseases, as they all initially present with ON in absence of other ophthalmologic findings. In these cases, it is recommended to refer or admit the patient to the ER for contrast-enhanced MRI of the brain, orbits and spine, in addition to NMO-IgG and anti-MOG.

Optometrists need to recognize the early signs of demyelinating disease in the eye. Rapid, accurate diagnosis




Bilateral retinal nerve fiber loss OU in a patient with MS without a history of ON.

will allow the patient to receive the appropriate treatments and have the best chance at maintaining vision and a high quality of life. ■

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FACTS AND FICTION ABOUT ADENOVIRAL CONJUNCTIVITIS

Here's what current research tells us about how to best diagnose and treat this highly transmissible infection.



BY TAMMY THAN, OD
DUBLIN, GA

Adenoviral conjunctivitis (Ad-Cs) is a prevalent, highly contagious condition that has considerable morbidity and economic impact. Despite this, there are no FDA-approved treatments for Ad-Cs. The off-label use of 5% povidone-iodine (PVP-I)—a broad-spectrum antiseptic with an excellent safety profile—has been adopted by some clinicians to treat patients with Ad-Cs. But how effective is this intervention really?

A pilot clinical trial—the Reducing Adenoviral Patient Infected Days (RAPID) study, completed in 2018—assessed if a single, in-office treatment with 5% PVP-I reduces virus-positive days more rapidly than artificial tears alone (n=28). This decade-long research project has provided numerous insights, including some you may not have suspected regarding the diagnosis and management of this challenging, terribly uncomfortable and potentially sight-threatening infection.

The following are members of the RAPID study steering committee and contributed to the research presented in this article:

- Tammy Than
- Mae Gordon
- Jennifer Harthan
- Andrew Hartwick
- Julia Huecker
- Spencer Johnson
- Mary Migneco
- Christina Morettin
- Christian Olson
- Ellen Shorter
- Meredith Whiteside

In this article, I'll discuss some of the main findings of the RAPID study and debunk a few myths about managing this infectious disease. But first, let's review what exactly a diagnosis of Ad-Cs means for you and your patient and the potential effects it can have on vision and the eye.

What is Ad-Cs?

Often referred to as “pink eye,” Ad-Cs is one of the most common eye infections worldwide. The proportion of infectious conjunctivitis cases that are due to viral infections may be as

high as 80%, and 65% to 90% of viral infections are thought to be a result of adenoviruses.¹ Patients with acute conjunctivitis typically present to a primary care provider, comprising as much as 2% of a general practitioner's practice.² A population-based incidence study of eye-related emergency department visits reported two million visits per year, with 28% of these visits being related to a diagnosis of acute or other types of conjunctivitis.³

Ad-Cs is more contagious than other forms of conjunctivitis partly due to the virus's ability to remain infectious in a desiccated state for weeks at room temperature.⁴ Adenoviruses have no outer lipid bilayer and are highly resistant to standard disinfectants, including 70% isopropyl alcohol and 3% hydrogen peroxide.⁵ The virus is transmitted directly through droplets or smears of infected bodily fluids, primarily tears or respiratory secretions and by fomites on towels, doorknobs, pens, counters, instruments, eye drops or eyeglasses.⁶

In a small study by Azar et al., the hands of nearly 50% of patients with Ad-Cs presenting for care were

About the author

Dr. Than is a staff optometrist at the Carl Vinson VA Medical Center in Dublin, Georgia. She was formerly a professor at the University of Alabama at Birmingham School of Optometry. Dr. Than publishes in several optometric journals and lectures nationally on various subjects including therapeutics, dermatology and ophthalmic lasers. She has received numerous optometry and teaching awards and is also a Fellow of the American Academy of Optometry. Dr. Than has no financial interests to disclose.

culture-positive, compared to 0% of patients who didn't have the infection.⁶ Secondary transmission of Ad-Cs to members of the same household is estimated to occur at a rate of 20%.⁷ Outbreaks frequently occur in schools, military units, nursing homes, workplaces and community and healthcare facilities.⁷⁻¹³

Due to the highly transmissible nature of the condition, its economic impact is a significant concern. An estimated \$670 million is spent annually on the medical management of Ad-Cs.¹⁴ Not only do companies likely suffer from the absence of multiple employees at once, but infected workers may also be forced to take a leave without pay until they are no longer symptomatic (which could take up to four weeks). One large study noted that infected workers typically receive a one- to two-week furlough, potentially causing a loss of 25% to 50% in monthly wages (of course, paid time off may vary by employer).¹⁵

Ocular Effects

Ad-Cs is highly symptomatic, causing discomfort, tearing, lid swelling, photophobia and decreased vision. Ocular signs include bulbar conjunctival redness, chemosis, follicular reaction and subconjunctival hemorrhage. Ad-Cs is also often associated with a palpable preauricular node. Ocular sequelae include the formation of pseudomembranes and subepithelial corneal infiltrates. Approximately 15% to 48% of Ad-Cs patients develop subepithelial corneal infiltrates, which can cause permanent corneal stromal scarring and may lead to vision loss.¹⁶⁻¹⁹ Clinicians typically use symptoms and clinical signs to diagnose Ad-Cs, but this is complicated by their variability in presence and severity among infected individuals.²⁰

The incubation period for adenoviral ocular infections is two to 14 days prior to symptom onset and symptoms typically persist for seven to 28 days.^{21,22} The period of



Fig. 1. A patient with unilateral adenoviral conjunctivitis.

contagion lasts approximately three weeks. Studies report that most eyes are culture-negative by 13 days after the onset of symptoms.^{15,23} The duration and severity of symptoms and complications differ among the more than 20 adenovirus serotypes associated with ocular infections; however, serotypes 8, 19, 37 and 53 are known to have the greatest epidemic potential.²⁴

Confirming the Diagnosis

An accurate diagnosis of Ad-Cs is essential for timely and appropriate management to reduce transmission, duration, severity and complications of Ad-Cs. However, a recent meta-analysis of 77 publications concluded that clinicians cannot reliably differentiate between bacterial and viral conjunctivitis based on clinical signs and symptoms.²⁵ In a systematic review of more than 6,800 publications, a study by Rietveld et al. was unable to find evidence of the clinical signs or symptoms that were useful for the differential diagnosis of bacterial from viral conjunctivitis.²⁶

The percentage of clinically diagnosed Ad-Cs cases for which adenoviral etiology is confirmed by polymerase chain reaction (PCR) testing is variable, with estimates ranging from 8% to 82%, highlighting the challenge of accurate diagnosis.^{14,27-31} While PCR testing is the gold standard for adenoviral detection, the technique is costly and time-consuming, usually requiring off-site testing that prevents

immediate diagnosis. In 2006, the FDA approved a CLIA-waived, point-of-care test for acute conjunctivitis called the QuickVue adenoviral conjunctivitis test (previously known as AdenoPlus; Quidel Corp.). In 10 minutes, this point-of-care test provides a binary “yes” or “no” result for the presence of adenovirus antigen down to a lower limit of 40 to 50 virions. Sensitivity has been reported to range from 40% to 93% and specificity from 81% to 98%.³³⁻³⁶

A survey of eyecare providers at a national meeting found that only 10% of the 340 attendees reported use of this point-of-care test. This highlights the current lack of a widely accepted, inexpensive, in-office test that can accurately determine the presence of Ad-Cs.³⁷

Treatment Options

Not only is it challenging to make an accurate diagnosis, the actual management of this form of conjunctivitis presents its own unique hurdles, as there aren't any FDA-approved treatments for Ad-Cs. Antibiotics are commonly prescribed for conjunctivitis regardless of causative agent.¹⁵ Analysis of claims data in a large managed care network found that nearly 60% of the patients diagnosed with acute conjunctivitis filled an antibiotic prescription, and 20% were prescribed an antibiotic-corticosteroid product.³⁸ Unnecessary or inappropriate use of antibiotics is partly attributable to the difficulty in discriminating between viral

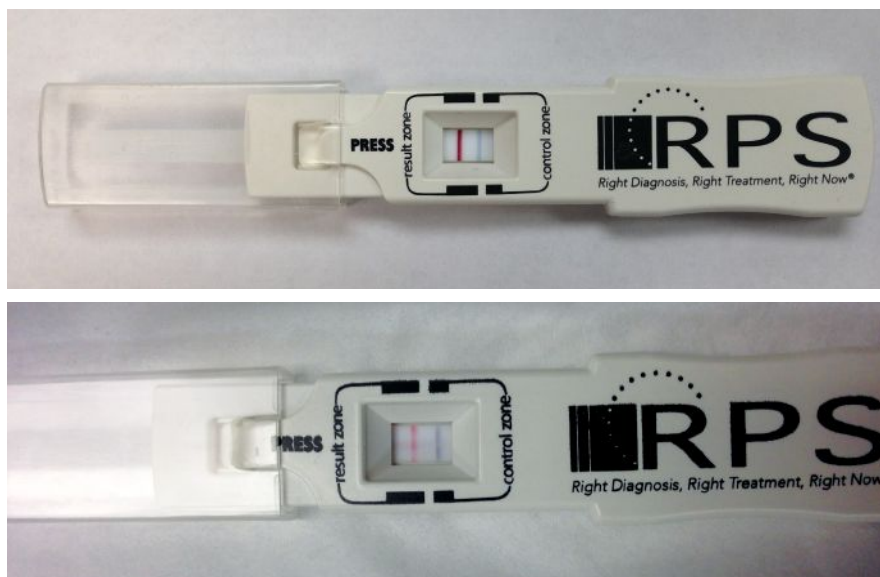


Fig. 2. Shown here are two positive point-of-care tests using the RPS Adeno Detector (Rapid Pathogen Screening). The blue line is the control; presence of the red line indicates a positive test result for Ad-Cs. The top image is prior to treatment with PVP-I; the bottom image is 24 hours post-treatment.

and bacterial conjunctivitis. Both the American Optometric Association clinical practice guidelines and American Academy of Ophthalmology preferred practice guidelines recommend supportive care consisting of artificial tears, topical antihistamines and cold compresses.^{39,40}

Several antiviral agents have been tested but the adenoviral structural characteristics have proven too hardy for these medications. Because of the significant morbidity and transmissibility associated with this form of conjunctivitis, there are ongoing drug development efforts to find an effective FDA-approved agent.

Until such a drug reaches market, several medications are being used off-label, including a one-time application of PVP-I. Iodine has been used as an antiseptic since 1839. An ophthalmic formulation of povidone-iodine is available at a concentration of 5% (Betadine 5%, Alcon) while the concentration u for dermatologic applications is 10% (Figure 3).

Ophthalmic PVP-I is FDA-approved for “the prepping of the periocular region (lids, brow and cheek) and irrigation of the ocular surface (cornea, conjunctiva and palpebral

fornices).” PVP-I has been shown to be effective against bacteria, including chlamydia, fungi and protozoa, as well as viruses, including adeno, herpes simplex and enteroviruses, without significant corneal or other ocular toxicity. Compared to other antiseptic agents, it has a wider virucidal spectrum.⁹

More than two decades ago, a study recommended that 5% PVP-I was a “good treatment for such external ocular infections as Ad-Cs.”⁴¹ This “off-label” use of 5% PVP-I as a treatment option for Ad-Cs has continued to gain credence, with its promotion in influential editorials and reviews that have wide distribution within the eyecare community.^{42,43} In their annual drug guide, Randall Thomas, OD, MPH, and Ron Melton, OD, recommend a protocol for using PVP-I based on their clinical experience and research (Figure 4).⁴⁴ This same regimen is recommended in other literature for treating cases of suspected COVID-19-related viral conjunctivitis, as PVP-I is effective against this virus as well.⁴⁵

Despite the lack of well-designed clinical studies, a 2013 survey of

more than 600 eyecare providers found that one-third used off-label 5% PVP-I as part of their management of Ad-Cs (Figure 5).³⁷ Only a few clinical trials have investigated the efficacy of PVP-I alone for Ad-Cs; more have assessed PVP-I in combination with dexamethasone. These studies suggest that PVP-I alone can effectively reduce viral titers, symptom severity and/or duration. Larger, double-masked, placebo-controlled randomized trials of fixed-combination PVP-I and dexamethasone have shown efficacy in reducing the severity and duration of Ad-Cs.

Earlier this year, a Cochrane review by Liu et al. found that the current available evidence is insufficient to determine whether any of the evaluated interventions including PVP-I confer an advantage over steroids or artificial tears with respect to virus eradication (epidemic keratoconjunctivitis) or its spread to initially uninvolved fellow eyes. However, data from the RAPID study concludes that this pharmaceutical in particular may have more merit as a treatment for Ad-Cs than previously shown.

The RAPID Study

In this pilot clinical trial funded by the National Institutes of Health and conducted by a team of colleagues and I, patients who presented with presumed Ad-Cs were screened at nine US clinics. They were eligible to be enrolled if they were at least 18 years old, had symptoms consistent with Ad-Cs for four days or less and had a positive point-of-care (Adeno-Plus) test.

Patients were randomized to receive a single administration in-office on the day of enrollment of 5% PVP-I or artificial tears in one eye. To avoid confounding factors, no topical steroids nor NSAIDs were used. Patients were to use preservative-free artificial tears four times daily while symptomatic. Serial quantitative polymerase chain

reaction (qPCR) analyses were performed to determine the impact of treatment on viral titers over a period of three weeks. Clinical signs and symptoms were assessed over the three-week period (days one to two, four, seven, 14 and 21) comparing the effect of PVP-I and artificial tears administered a single time in-office. The primary outcome was percent reduction from peak viral load. Secondary outcomes were improvement in clinical signs and symptoms. Some of the study's conclusions are discussed in the next section.

Ad-Cs: Fact or Fiction?

Let's dissect a few common myths—or truths—about Ad-Cs using findings from the RAPID study and other current literature. Test your clinical understanding and see how many of the following factual or fictitious statements about the condition may come as a surprise to you.

1. The majority of conjunctivitis is caused by adenovirus. *FICTION!*

In our study, we recruited patients suspected of having Ad-Cs based on a set of commonly accepted, predetermined clinical signs and symptoms. Of the 212 screened, only 56 had a positive point-of-care test (26.4%). Of those 56, only 28 had the presence of adenoviral titers based on qPCR. Therefore, of the 212 presenting with presumed Ad-Cs, in fact only 13.2% were true positives (28 out of 212).

The literature reports a wide range of prevalence, but one large study at Johns Hopkins University with 1,520 individuals with suspected Ad-Cs demonstrated a surprisingly low percentage—only 8.6%—were positive for adenovirus through PCR testing.⁴⁶

Studies by Kam and Holtz report PCR-confirmed diagnoses in patients presenting with presumed Ad-Cs are 39.4% and 21.7%, respectively.⁴⁶ These results indicate that many patients suspected to have Ad-Cs based on clinical signs and symptoms

are likely unnecessarily quarantined. The question of what causes the more than 80% of presumed Ad-Cs cases remains yet to be answered. One possible cause is some other viral infection, but further research is needed.

2. Betadine is intolerable and therefore not a good option for patients. *FICTION!*

While *in vitro* and animal models of PVP-I have demonstrated corneal epithelial cell toxicity, several study limitations challenge the validity of these findings. For example, the PVP-I concentrations used were much higher than what is used clinically, ophthalmic formulations were not used and, in two studies particularly, PVP-I was injected directly into the anterior chamber.¹⁴ A small study of 10 healthy normal subjects reported corneal epithelial changes after application of 5% PVP-I that resolved within 24 hours. Another study, by Saedon et al., reported increased dry eye symptoms and corneal epithelial staining in eyes that received multiple intravitreal injections preceded by PVP-I; however, the eyes were compared to fellow eyes receiving neither intravitreal injections nor PVP-I.⁴⁷⁻⁴⁹

According to Marks, the safety of PVP-I has been demonstrated by the lack of reports of significant toxicity or poor tolerability in animals and humans.⁵⁰ In the RAPID study, corneal staining increased immediately post-administration of PVP-I but returned to baseline levels within hours. There was no change in visual acuity between baseline and day one. It was reassuring

to note that there was no change in participant-rated overall discomfort immediately post-administration of PVP-I or on day one compared to baseline. These results suggest ophthalmic 5% PVP-I used as a one-time treatment is safe and well tolerated by patients with Ad-Cs. Assessment of the effectiveness of masking provides additional implicit evidence of PVP-I tolerability. During informed consent, the study patients were educated regarding the potential stinging of PVP-I.

All treated patients were asked immediately following in-office treatment as to whether they believed they received PVP-I, artificial tears or were not sure. Thirty-four percent of participants treated with PVP-I guessed incorrectly or were unsure which treatment they received. Presumably if PVP-I caused significant discomfort upon instillation, participants would have had a much higher correct-guess rate.⁵¹

3. QuickVue adenoviral conjunctivitis test has no clinical utility. *FICTION!*

This point-of-care test had relatively low-positive predictive power for Ad-Cs, as only 50% of the point-of-care test-positive patients had viral titers on qPCR testing.³⁶ This is consistent with some of the previous reports.

Considering this data in isolation, one would presume that this point-of-care test is no better than random chance. However, where the value of this test lies is in its excellent negative predictive power; 98% of those that were negative on point-of-care testing did not have presence of viral load on qPCR testing. This finding has clinical implications, as negative test

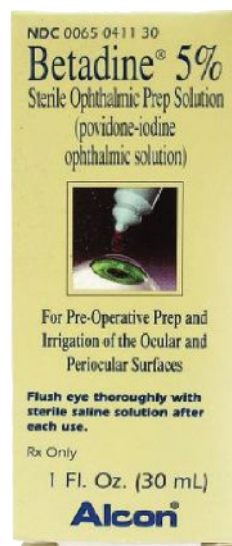


Fig. 3. Ophthalmic formulation of PVP-I.

PVP-I Treatment Protocol for Ad-Cs⁴⁴

- Anesthetize with proparacaine
- Instill one or two drops of NSAID
- Instill several drops Betadine 5% in eye(s); close eye(s)
- Swab or rub excess over lid margin
- After 60 to 90 seconds, irrigate with sterile saline
- Instill one or two drops of NSAID
- Rx steroid QID for four days

Fig. 4. Protocol of Drs. Melton and Thomas. In an effort to minimize confounding factors, RAPID study did not use topical NSAID or steroid, used a contact time of two minutes and prescribed preservative-free artificial tears four times a day.

results can indicate non-adenoviral etiology to the clinician, greatly altering management and quarantine recommendations. Confirmation that the conjunctivitis is not adenoviral has significant economic impact by avoiding the need to take time off work.

4. Betadine prevents the formation of SEIs and pseudomembranes. FICTION!

It was hypothesized that 5% PVP-I would reduce the incidence of ocular sequelae of Ad-Cs consistent with what was anecdotally observed prior to this study. However, the incidence of corneal infiltrates and pseudomembranes was higher in the 5% PVP-I group compared to those receiving artificial tears, although not statistically significant. Fourteen of 25 participants (56%) who were qPCR-positive for adenovirus developed either a subepithelial infiltrate (seven in the PVP-I group and four in the artificial tear group) or a pseudomembrane (three in the PVP-I group and one in the artificial tear group). One participant had both complications. These findings were not expected, and the small sample size makes interpretation challenging. Still, these results show that a one-time in-office application of 5% PVP-I clearly did not prevent ocular sequelae of Ad-Cs.

The overall incidence (both treatment groups) of pseudomembranes

in our study was 16%, which is comparable to the 24% reported by Butt et al. in a retrospective observational study.⁵² The incidence of infiltrates was 56% in this study and is consistent with the Lee et al. prospective study of 500 patients in four countries, which reported an incidence of 59% over 18 days of follow-up.³² A retrospective study of 110 patients in the United States reported an incidence of infiltrates of 49%.⁵² Serotyping was not performed, though that information may have been useful in identifying which serotypes were associated with development of infiltrates or pseudomembranes.

5. Resolution of signs and symptoms of Ad-Cs indicate viral clearance. FICTION!

Resolution of Ad-Cs is typically determined either based on the “typical” time course of the disease or by monitoring for clearing of key signs and symptoms. Because of the nature of this study, we were able to perform qPCR testing from each visit (which is impractical in a clinical setting) analyzing the relationship of viral titers to clinical signs and symptoms. Not surprisingly, higher baseline viral titers resulted in more severe symptoms and signs and these cases took longer for viral clearance. It was found that most signs and symptoms persisted after viral clearance.

Of all the signs and symptoms typically used clinically to aid in the diagnosis of Ad-Cs, it appears that the disappearance of serous discharge most closely correlates with the viral clearance. Using the resolution of signs and symptoms (other than serous discharge) to determine when patients are no longer contagious likely results in delayed release from quarantine.

In another analysis, researchers found that viral titers are detected by qPCR after the point-of-care testing yields negative results. So, even though the point-of-care test is more accessible, cheaper and provides nearly immediate results (10 minutes), patients with Ad-Cs may still have detectable virus more than 14 days after initial presentation. This highlights the need for development of a rapid, inexpensive method for assessing viral titers.

6. Lymph nodes are present in the majority of Ad-Cs cases. FICTION!

Classic training has taught clinicians to expect most if not all patients presenting with Ad-Cs will have a preauricular node. Our study found 46% of those with qPCR confirmed Ad-Cs to have a preauricular node at initial presentation. Nodal involvement increased to 56% if other palpated nodes (e.g., retroauricular, submandibular) were included. This still indicates that a significant number of Ad-Cs cases do not present with the classic preauricular node, so its absence doesn’t rule the disease out as one of several potential diagnoses.

7. Eyelid swelling is more useful than follicles in diagnosing Ad-Cs. FACT!

Using multivariate modeling, clinician-graded conjunctival redness, participant-reported eyelid edema and overall discomfort were the three clinical findings that were highly predictive in identifying individuals with PCR-confirmed Ad-Cs.⁵³ Combining the scores of these three clinical signs/symptoms with the results of an adenoviral






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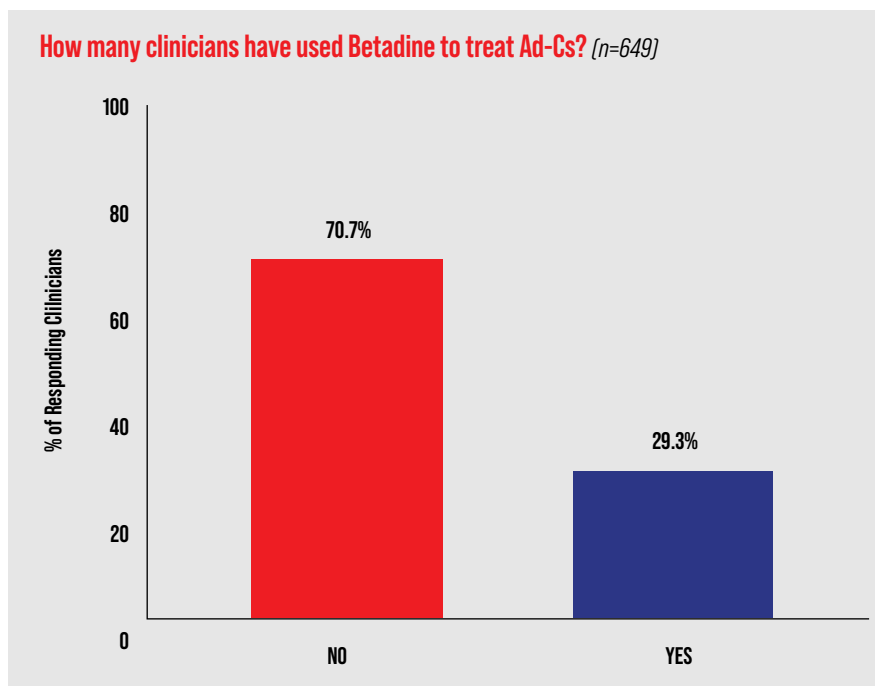


Fig. 5. PVP-I usage by optometrists and ophthalmologists for presumed Ad-Cs. This data comes from the survey responses of 649 clinicians from seven eyecare meetings in 2013.³⁷

point-of-care test further improved the predictive accuracy of correctly identifying Ad-Cs. This may appear confusing based on the apparent inaccuracy of the point-of-care test; however, when combined with key clinical signs and symptoms, the predictive ability of the presence of Ad-Cs improved significantly. Improving diagnostic accuracy for Ad-Cs by incorporating both point-of-care tests and clinical evaluation of key signs and symptoms could prevent unnecessary work furloughs and facilitate earlier management decisions for clinicians.

8. PVP-I has no value in management of Ad-Cs. YOU BE THE JUDGE!

Four days after treatment in the RAPID study, viral titers in the 5% PVP-I and artificial tear groups were 2.5% ± 2.7% and 14.4% ± 10.5% of peak, respectively (Figure 6).²⁰ Severity of patient-reported symptoms as well as clinician-graded signs were lower in the 5% PVP-I group than artificial tear group on day four. After day four, viral titers and severity of signs and symptoms decreased mark-

edly in both groups and no differences between groups were detected.

Bottom line is that PVP-I, while not perhaps as robust as previously thought, resulted in patients feeling and looking better at day four, which

is consistent with reduced viral load. After that time point, the resolution parallels the natural course. Based on this observation, it appears that offering PVP-I to patients presenting early in the course of the disease is warranted.

Takeaways

These two words sum up our conclusions about the use of PVP-I: *educate* and *offer*. Until we have a rapid PCR test available and an FDA-approved medication for Ad-Cs, we can use the knowledge gained from current literature such as the RAPID study to help guide management of infected patients, who should also be informed of their therapeutic options. In addition to PVP-I, supportive care such as artificial tears and cool compresses is still warranted. Other medications such as topical steroids, NSAIDs and topical ganciclovir continue to be used off-label in the management of Ad-Cs.

The next time a patient presents to your office with presumed Ad-Cs, consider using the point-of-care test. If negative, you be quite confident (with 98% certainty) that it's not

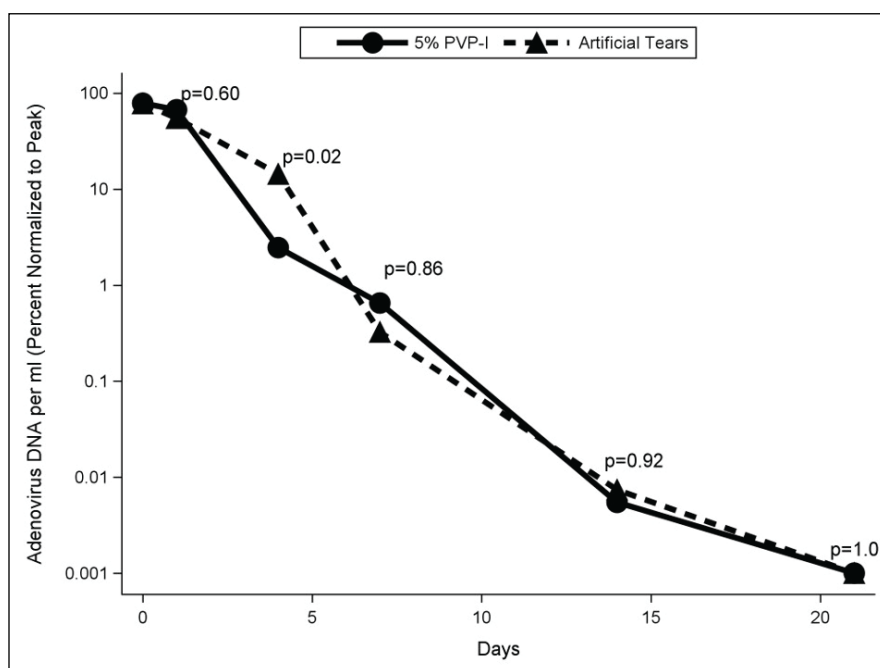


Fig. 6. Percent of peak viral load for 5% PVP-I and artificial tears groups at days one to two, four, seven, 14 and 21 among participants qPCR + for adenovirus.



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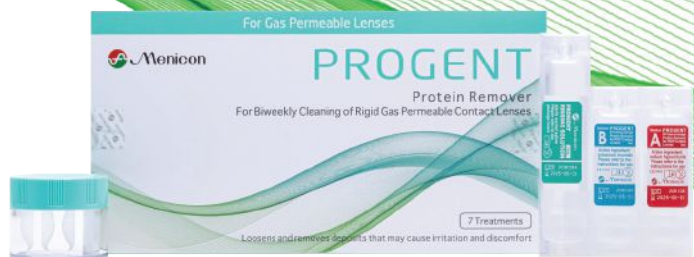
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Epidemic keratoconjunctivitis in a 30-year-old woman.

Ad-Cs. If positive, there is a greater chance that it is Ad-Cs. Consider offering PVP-I to your patients with adenoviral keratoconjunctivitis to help them feel better sooner, keeping in mind that infiltrates may still occur. ■

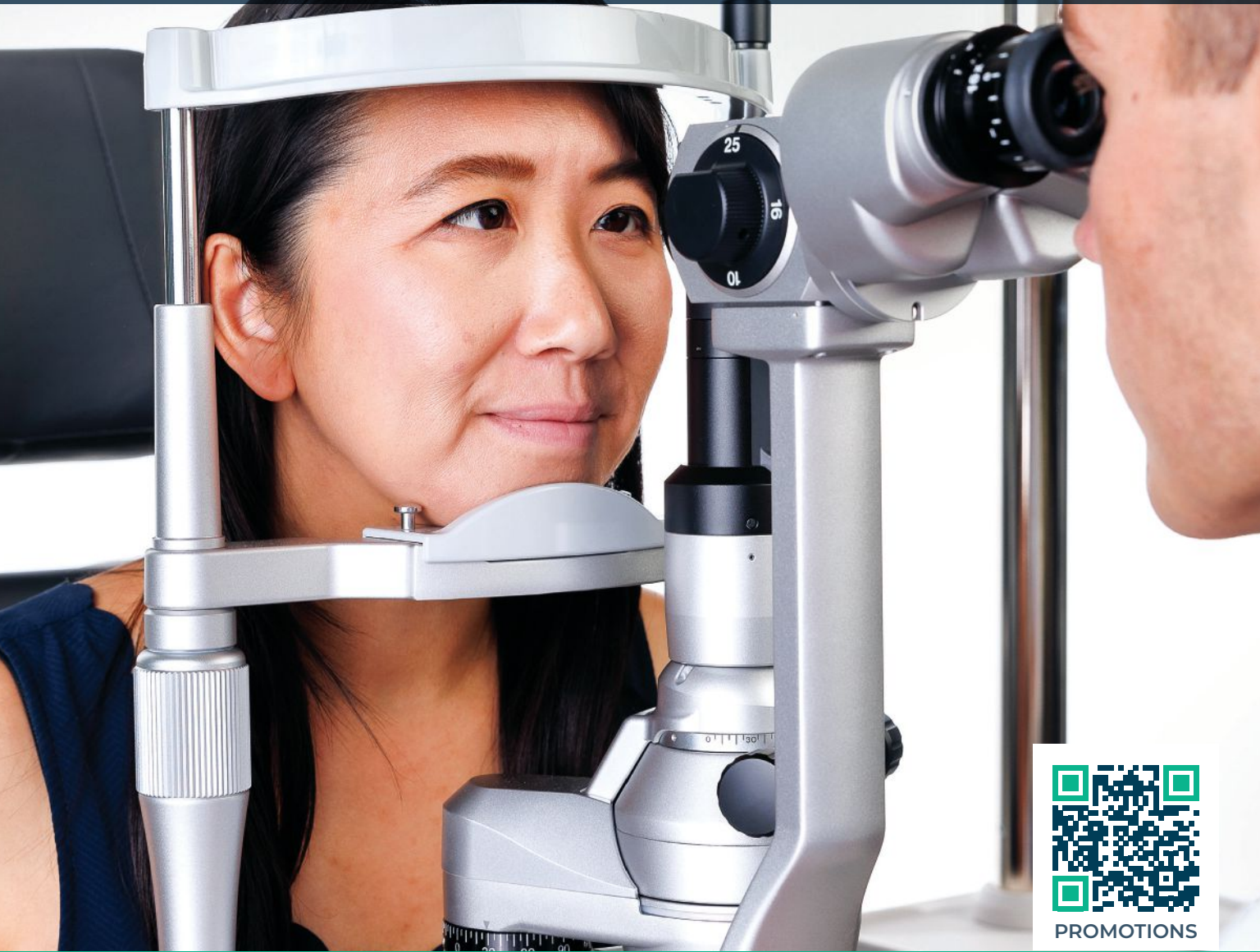
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DON'T UNDERESTIMATE *DEMODEX*

The mite is prevalent enough that it warrants more discussion and attention to treatment. With a promising clinical trial underway, now may be its time.



BY CECELIA KOETTING, OD
DENVER

D*emodex* mites are the most common ectoparasites on humans and, because of their ubiquity, this species has largely been ignored as human pathogens. Mites are typically harmless and exist in various environments on the body, but when there is an overpopulation, as evidenced by collarettes on the eyelashes, they may go from being benign to causing inflammation and a variety of diseases. They have been associated with acne vulgaris, folliculitis, rosacea, seborrheic dermatitis and hair loss among other conditions.¹ Specific to the eye, they have been implicated in diseases of the eyelid and lid margin, including blepharitis and meibomian gland dysfunction (MGD).¹

Prevalence

A study published in 2022 involving over 1,000 consecutive eyecare patients found that 57.7% had *Demodex* blepharitis.² Other studies have



Photo: Patrick Vollmer, OD

A close-up microscopy photo of a *Demodex* mite enjoying a meal of paracilia debris.

indicated that there is an increase in *Demodex* blepharitis with age, with the highest rate occurring between ages 20 and 30. This is suspected to be because sebum secretion is at its highest during this period.³ Another spike in occurrence is experienced by patients over the age of 60, likely related to dermatochalasis and skin pH changes.

It also believed that the increase in *Demodex* blepharitis found in children under the age of five is related to their constant touching of the face, which introduces bacteria to the skin.³ Initial exposure to *Demodex* occurs at birth or shortly thereafter by skin-to-skin contact between parent and newborn.³ Sebum secretion in 20- to 30-year-olds, dermatochalasis

About the author

Dr. Koetting practices at MD/OD practice Hines Sight in Denver, CO. Her primary focus is in anterior segment and ocular surface disease, neuro-optometry and perioperative care. Dr. Koetting is fellow in the American Academy of Optometry, a diplomate of the American Board of Optometry, active member of AOA and has served as both local and state officers in AOA. She was named young optometrist of the year in 2019 by the state of Virginia, receiving the Vanguard of the Year Award. Dr. Koetting lectures locally, nationally and internationally at conferences and has written for multiple publications.

in those over 60 and increased facial touching of young children are all instances of which *Demodex* overpopulation becomes an increased risk, thus concern broadly spans all age groups. Increased mite population is also more common in patients with rosacea.³

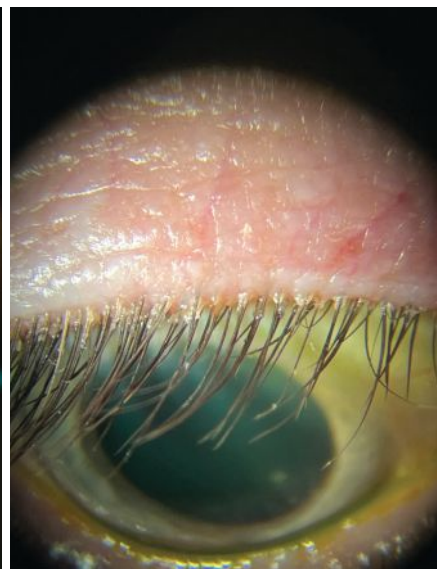
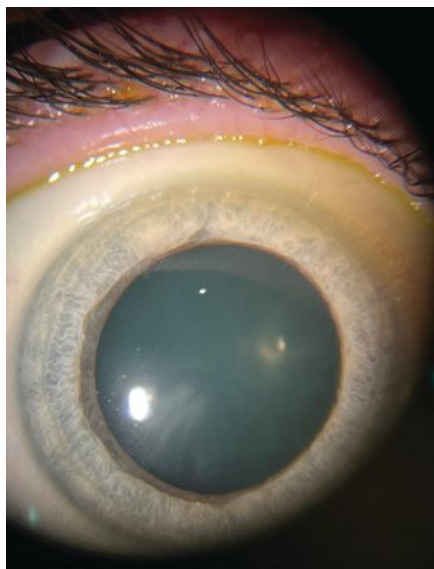
Anatomy of the Enemy

There are two known species of *Demodex* that affect the eye: *Demodex folliculorum* and *Demodex brevis*. *Demodex folliculorum* organisms are typically 0.30mm to 0.40mm in length and are typically found in clusters around the lash root and lash follicle, feeding on sebum and follicular epithelial cells.^{1,3-5} *Demodex brevis* is slightly smaller at 0.15mm to 0.20mm in length and typically travels alone, preferring to infest the meibomian glands.^{1,3-5} Both species have semi-translucent, elongated bodies with two segments. They have eight short-clawed legs, allowing them to move at a rate of 8mm to 16mm an hour; they are most often active at night.^{1,3-5} They can anchor into the hair follicle with the help of their scales, and their pin-like mouths aid in eating skin cells, oils and bacteria.^{1,4-5}

Demodex typically mate within the hair follicle opening and lay their eggs within the follicle or sebaceous gland. The larvae hatch three to four days later and develop into adults within seven days. They have an approximate lifecycle of 14 days. Their total lifespan is two to three weeks and the dead mites are left to decompose inside the follicle or sebaceous gland.^{1,4-5}

Demodex Causes Trouble

Infestation of these creatures causes both ocular surface disease and meibomian gland dysfunction to worsen. The related mechanisms are believed to be mechanical, bacterial and inflammatory. While *Demodex* mites consume epithelial cells at the hair follicle, they can cause follicular distention. Microabrasions caused



These photos are of the same patient during slit lamp exam. The left photo is of the patient looking straight ahead with minimal identifiable blepharitis. The right photo is the patient looking down with obvious collarettes, indicating a *Demodex* infestation.

by the mites' claws further induce epithelial hyperplasia and reactive hyperkeratinization.

D. brevis, preferring the meibomian glands, can cause blocking of the orifices. Their chitinous exoskeleton acts as a foreign body, causing a granulomatous reaction. In theory, this is a potential cause of chalazia and MGD. *Demodex* carry bacteria within their gut that is released with excrement and in death, as well as harboring bacteria on their surface. Bacteria from either of these sources leads to infection. A delayed hypersensitivity to these proteins carried within the mites' debris and waste causes an inflammatory response.

Infestation Manifestation

These infestations most commonly lead to patient complaints of itching, burning, tearing, redness, crusting or stickiness of eyelids, although patients often remain asymptomatic. Relying solely on patient complaints to diagnose *Demodex* infestation can lead to significant misdiagnosis and lack of appropriate treatment.

Collarettes, which are translucent waxy plugs at the base of the lashes, are the pathognomonic sign of an overpopulation of *Demodex*.⁶⁻⁸ One

clinical study showed that *Demodex* mites were found on 100% of lashes with collarettes.¹ They are composed of regurgitated and undigested material, epithelial cells, keratin, mite eggs and digestive enzymes.^{7,8}

The best way to identify collarettes is on slit lamp exam. When examining the lids, remember to look, lift, push and pull. Asking your patient to look down when examining the lid margin can reveal diffuse collarettes and misdirected or missing lashes that otherwise would have gone unseen. Take the time to then look at the lid margin, inspecting for saponification, lid margin debris or biofilm, telangiectasia and lid margin thickening. Next, push on the meibomian glands to grade both expressibility and meibum quality. Studies have shown that MGD is significantly more prevalent in conjunction with *Demodex* infestations.⁴

It is worth mentioning that an overpopulation of *Demodex* and blepharitis can also lead to a higher rate of contact lens intolerance and subsequent dropout in patients. A 2015 study found that 90% of contact lens wearers were positive for *Demodex* in comparison with only 65% of non-wearers.⁹ Furthermore, a separate

PATIENT DISCUSSION TIPS

It can be difficult for many of us to have the conversation about *Demodex* without feeling like we are “bugging” out our patients or even ourselves. Unfortunately, there is no way around the truth, but how you deliver the message can make all the difference to help stick a better landing. Here is an example of how to discuss this issue:

“Mr. Smith, overall your eyes are looking very healthy on today’s exam. However, I am noticing an overgrowth of bacteria and mites on the eyelashes today. Both mites and bacteria are normally found on the eyelashes, just like bacteria is on our faces and in our mouths. We do things like brushing our teeth and washing our faces to keep them under control. Similarly with the eyes, when these two get out of balance, they can start to cause problems like inflammation or itchiness. I’m going to start you on at-home treatment to help restore that balance.”

study found that approximately 93% of patients with contact lens intolerance were also positive for *Demodex*.¹⁰

Disease Management

Demodex blepharitis management techniques currently revolve around improving eyelid hygiene. The idea is to control bacterial overgrowth, which can be a food source for the mites. Good lid hygiene using lid sprays or wipes containing hypochlorous acid can help to keep bacterial, fungal and viral pathogens of the eyelids under control.¹ Oral doxycycline and azithromycin are effective in use for treatment of MGD.¹¹

Focus has been on tea tree oil for several years as a management option for active *Demodex* infestations. The mites are resistant to many antiseptic agents, such as alcohol, povidone-iodine and erythromycin.¹ Tea tree oil, while not always effective or well-tolerated, is commonly used due to lack of FDA approved treatments and is subsequently the go-to option.¹ The oil helps remove the collarettes from the eyelash roots, kill some of the mites and stimulates

the buried mites to migrate up to the skin surface.⁴ Unfortunately, studies have not been able to show full eradication of *Demodex* after four weeks of tea tree oil-derived therapy, even when blepharoexfoliation was used to debulk the infestation.¹⁴

Another promising management option is okra extract. It has antioxidative and anti-inflammatory effects on the Akt-mediated NF-κB pathway involved in dry eye and blepharitis.¹² One study compared the use of okra eyelid patches and tea tree oil eyelid patches, finding similar survival time of the *Demodex* in both groups at 115.3 minutes and 106.7 minutes, respectively.¹² However, tolerance in the okra group was considerably better than that of the tea tree oil subjects.¹² Thus, okra extract seems a management technique that may be better suited for sensitive patients.

Manuka honey is known for its anti-inflammatory and antimicrobial properties because of its low pH, high osmolarity and high methylglyoxal (MGO) content.¹³ MGO is found in other honey varieties but is higher in concentration in New Zealand Manuka honey.¹³ A 2020 study used Manuka eye cream overnight for three months in patients with blepharitis, finding significant improvements in ocular surface symptomatology, tear film stability, bacterial load and signs of ocular *Demodex* infestation.¹³

On the Horizon

Data from two double masked, randomized Phase III pivotal studies, comprising 833 patients, was released earlier this year on studies of the use of lotilaner ophthalmic solution 0.25% (TP-03, Tarsus) for this condition. The researchers regarded the intervention as an effective and safe treatment for *Demodex* blepharitis.¹⁴ Patients were given one drop of TP-03 twice a day for six weeks and were required to have at least 10 collarettes per lid at the time of enrollment.¹⁴

In the most recent study, Saturn-2, the primary endpoint of complete collarette cure (zero to two collarettes per lid at day 43) was achieved in 56% of patients, and an astounding 89% of patients had 10 or fewer collarettes.¹⁴ The secondary endpoint of mite eradication (zero mites per lash) was met in 52% of patients, while lid erythema cure was found in 31.1% of patients.¹⁴ The treatment was well tolerated by patients, as 91% reported that drop comfort was neutral to very comfortable.¹⁴

This is very promising data, and soon we may have a better treatment option for our patients with *Demodex* blepharitis that will have proven safety, tolerability and effectiveness in collarette reduction and mite eradication. Until then, encouraging better lid hygiene and recommending blepharoexfoliation can provide some measure of relief. ■

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HOW SYSTEMIC DRUGS TRIGGER DRY EYE DISEASE

More than 20% of the most popular oral agents in health care impact the ocular surface. Find out which are the biggest offenders and what to do about it.



BY CARLA GILBERTSON KUIKEN, OD AND ERICA VANDERPOOL, OD
BATTLE CREEK, MI

With a rising incidence of over 20 million affected people in the United States alone, dry eye disease (DED) is now considered a major ocular condition.¹ DED affects patients of all ages and has been shown to negatively impact a patient's quality of life both physically and psychologically.² Increased awareness has led to significant worldwide progress in research, but dry eye management can be frustrating for both patients and clinicians alike. Significant strides have been made in not only defining and classifying DED, but also understanding the association between the condition, systemic comorbidities and systemic medications. The focus of this article will be iatrogenic DED; specifically, dry eye induced by systemic medications.

The definition of DED was carefully rewritten during publication of the 2017 report by the Tear Film & Ocular Surface Society's Dry Eye

Workshop II (DEWS II). The ultimate result: *"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."*³ This loss of homeostasis is the common denominator of all dry eye subtypes.¹

According to the latest *Physician's Desk Reference*, 22 out of the top 100 best-selling systemic drugs in the US were shown to possibly cause dry eye.⁴ Additionally, eight out of the nine systemic drugs that are secreted into the tear film are associated with induced dry eye, including common over-the-counter (OTC) meds aspirin and ibuprofen.⁴ Systemic medications may cause DED through decreased tear production, inflammatory effects on secretory glands, altered nerve input and reflex secretion or direct irritation through secretion into the tears.⁵

Numerous classes of pharmaceuticals can trigger DED, so the list of medications associated with dry eye is quite extensive. A thorough patient

history and medication review is crucial because myriad drugs, ranging from OTC medications to complex oncology and neurological agents, may affect the ocular surface. The DEWS II Iatrogenic Report provides a table of 171 systemic medications that are known or suspected to cause, contribute to or aggravate dry eye.⁵ However, bear in mind that much of the research is inconclusive and only 48 of the 171 medications are actually proven to be causative of DED.⁵

This article will review and give common examples of many of the medications from this list by class, discuss the mechanism of causation and offer approaches to management and treatment.

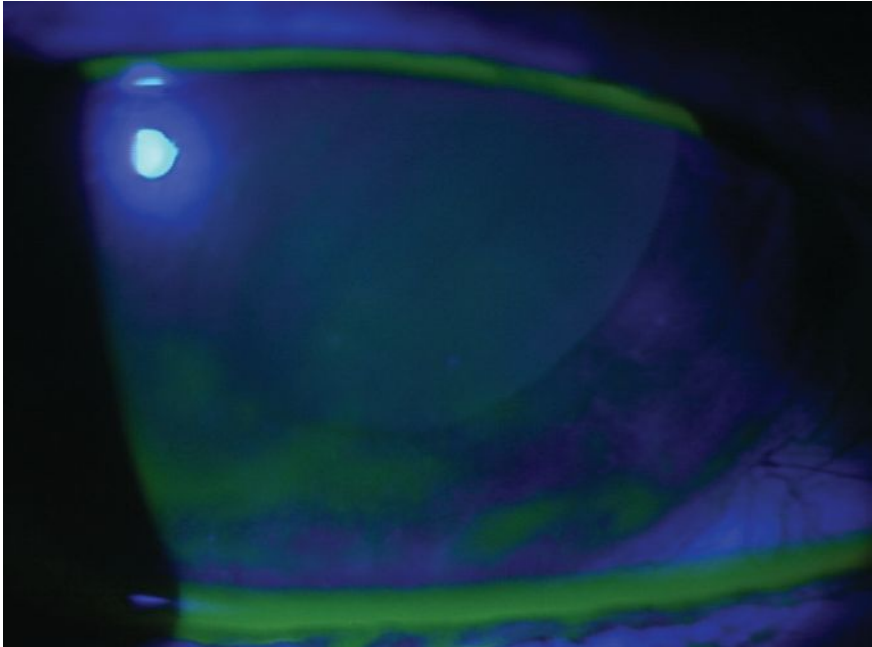
Anticholinergics

This is the largest category of systemic medications associated with dry eye, and the anticholinergics discussed in this article include antihistamines/decongestants, antidepressants, anti-Parkinson's, antipsychotics and antispasmodic medications.⁵

Most anticholinergic medications are antimuscarinic, as they competi-

About the authors

Dr. Gilbertson Kuiken is an attending optometrist at the Battle Creek Veterans Affairs Medical Center where she completed her ocular disease residency in 2012. She is a fellow of the American Academy of Optometry and maintains ABCMO certification. **Dr. Vanderpool** is a fellow of the American Academy of Optometry. She completed her residency in ocular disease at the Battle Creek Veterans Affairs Medical Center, where she has been an attending optometrist for the past five years. They have no financial disclosures.



A photo demonstrating a classic presentation of dry eye with superficial punctate keratitis, greatest inferiorly.

tively inhibit the binding of acetylcholine at post-synaptic muscarinic receptors.⁶ In terms of DED, this action decreases both aqueous and mucus tear secretions from lacrimal gland and conjunctival goblet cell receptors. With decreased tear volume and quality, the stability of the tear film is lost.^{5,6}

• **Antihistamines and Decongestants.** Commonly used and self-prescribed in many cases, antihistamines decrease tear production through reduction of aqueous outflow. From a DED perspective, it is better to prescribe or recommend second-generation antihistamines (*e.g.*, Clarin, Zyrtec, Allegra) rather than first generation. Second-gen antihistamines have less anticholinergic side effects because they more selectively bind to muscarinic receptors.⁶ Commonly prescribed H1-antihistamines for allergies include diphenhydramine (first generation), loratadine (second generation) and cetirizine (second generation).⁷

Those H1-antihistamine agents may be found in combination with decongestant medications. Decongestants cause local vasoconstriction,

which alters the blood flow to the lacrimal system, ultimately leading to reduced tear production.^{6,8} Pseudoephedrine (*e.g.*, Sudafed) is the most commonly used decongestant.⁷

H2-antihistamines are prescribed for stomach, esophageal and intestinal issues. Since these drugs also affect the muscarinic receptors, DED can be induced. Common examples are cimetidine (Tagamet) and famotidine (Pepcid AC).⁶

• **Antidepressants.** Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) all have been found to cause DED; they affect amine neurotransmitters. TCAs are well known to have anticholinergic effects, whereas SSRIs and SNRIs do not typically act as antimuscarinic agents despite showing increases in DED.

Both TCAs and SNRIs block serotonin and norepinephrine reuptake at the pre-synaptic neuron, ultimately leading to an increase in synaptic neurotransmission of serotonin and norepinephrine. SSRIs exclusively block serotonin reabsorption, increasing the level of serotonin concentrations bind-

ing to the post-synaptic receptors.^{5,6,9}

No clinical studies to date have specified which antidepressant would be best prescribed for patients suffering from DED; however, based on conclusions drawn from studies on antidepressants and dry mouth, it is suggested that SSRIs affect tear film homeostasis less than TCAs.^{6,10} Better still are SNRIs, which have less dry eye associations than their SSRI counterparts.¹⁰

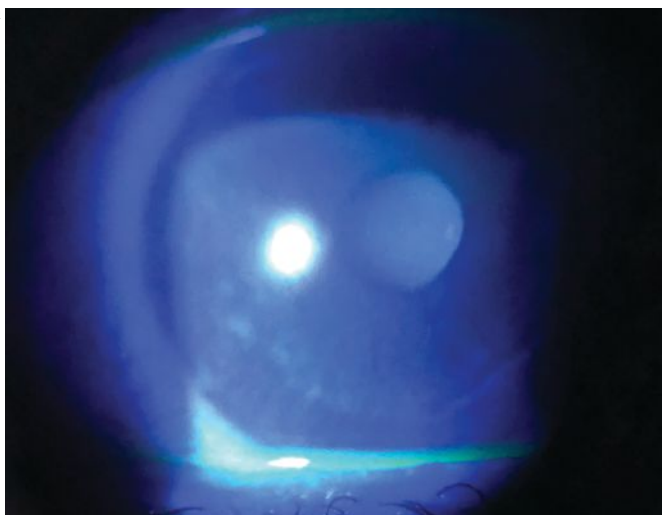
The most popular TCA prescribed is amitriptyline. Common SSRIs are sertraline (Zoloft), fluoxetine (Prozac), citalopram (Celexa) and escitalopram (Lexapro). Frequently prescribed SNRI antidepressants are duloxetine (Cymbalta) and venlafaxine (Effexor).⁷

• **Anti-Parkinson's drugs.** Initially, the movement disorder Parkinson's disease was treated with anticholinergics like benztropine and benzhexol. These drugs are now often used in conjunction with the favored anti-Parkinson medication levodopa, which may cause similar side effects to anticholinergic agents.⁶ Both in monotherapy and combination therapy, anti-Parkinson's medications act comparably to their antidepressant and antipsychotic counterparts regarding their impact on DED.¹¹

• **Antipsychotics.** These powerful drugs are classically divided into two groups: *typical*, which primarily affects dopamine receptors, and *atypical*, which primarily affects serotonergic receptors. Meds in both groups have anticholinergic effects, but there are no studies to determine which specific drugs are better or worse for DED. Investigative studies regarding antipsychotics and dry mouth did not favor the typical or atypical group as a whole, but rather suggested that there are certain drugs in each category that seemed to have less anticholinergic peripheral side effects.

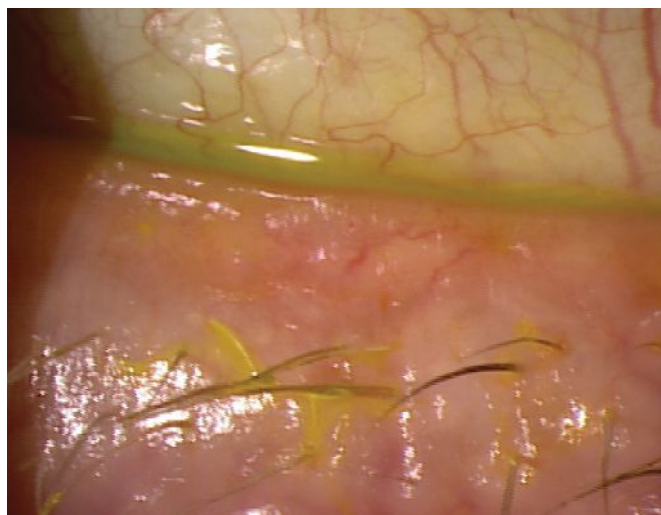
Of note, anticholinergic levels that affect the central nervous system do not correlate with anticholinergic levels in the serum.⁶ Current commonly used antipsychotic medications are

Photo: Juan Ding, OD



Dry eye in a patient with melanoma taking chemotherapeutic medications.

Photo: Brian Dornbos, OD



A polypharmacy patient with dryness associated with meibomian gland dysfunction.

haloperidol (typical), perphenazine (typical), quetiapine fumarate (atypical) and aripiprazole (atypical).^{5,7}

• **Antispasmodics.** These drugs are used to treat overactive bladder by acting on muscarinic receptors. Inadvertently, their antimuscarinic properties lead to DED. Antispasmodics shown to cause DED symptoms are oxybutynin, tolterodine and fesoterodine.^{5,6}

Antihypertensives

Of the four major classes of antihypertensive drugs, beta blockers and diuretics are known to induce dry eye. Beta blockers, which are adrenergic blocking, reduce aqueous production by lowering immunoglobulin A and lysozyme levels.^{11,12} Thiazide diuretics increase elimination of water and electrolytes, while loop diuretics reabsorb sodium. Both act on the kidney and reduce fluid availability throughout the body.⁸ With less overall fluid available to form tears, tear production is decreased.^{8,12}

Popularly prescribed systemic beta blockers include metoprolol, atenolol, carvedilol and propranolol. Common diuretics include hydrochlorothiazide and furosemide.⁷

Hormonal Therapies

Investigative research regarding the role sex hormones play in DED is inconclusive, as some studies show

benefits with hormone replacement therapy and others find worsening of dry eye signs and symptoms with these drugs. Combination estrogen and progesterone therapy during menopause can cause level imbalances that affect lacrimal function, but the effect of this combination therapy on DED is likely indirect.

Estrogen and progesterone are androgen-blocking agents, leading to decreased androgen levels and increased inflammation of the ocular surface. Oral contraceptives, which typically contain both estrogen and progesterone, have been specifically linked to meibomian gland dysfunction (MGD) associated dry eye.¹³ Two other popular hormonal medications that are associated with DED include tamsulosin and terazosin.⁵

Anticancer Drugs

Chemotherapeutic agents cannot differentiate between cancer cells and healthy cells. Consequently, the lacrimal glands are often affected, leading to the development of dry eye.⁸ Many anticancer medications also decrease stability of the ocular surface by disrupting the homeostasis of the cornea, conjunctiva and lacrimal system.¹⁴

Examples of these chemotherapeutic agents are methotrexate, mitomycin C, busulfan and cetuximab.⁵

Antiulcer Drugs

Recently, proton pump inhibitors (PPIs) have been linked to DED. The exact mechanism is unknown, but it is believed that long-term use of PPIs affects the absorption of vitamin B12, increasing risk of B12 deficiency and associated dry eye. Furthermore, PPIs affect the gut microbiome, which also maintains mucosal immune function outside the gut, and may ultimately impact the conjunctival microbiome.¹⁵

Omeprazole (Prilosec), one of the top 10 prescribed drugs in the US—available both OTC and with a prescription—is part of this medication class. Pantoprazole (Protonix) and esomeprazole (Nexium) are also commonly used PPIs.⁷

Anti-Acne Drugs

Most retinoids, a class of compounds derived from vitamin A, are topical. Isotretinoin, however, is a well-known oral retinoid used to treat acne; unfortunately, it is also causative for DED. Its mechanism of action causes unintended programmed cell death of sebaceous glands, which ultimately leads to disruption of the ocular surface through MGD and loss.^{6,16-17}

Analgesics

Aspirin and ibuprofen continue to be linked to dry eye. Both of these drugs

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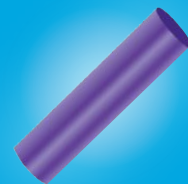


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* Sulley A, Young G, Hunt C. Factors in the success of new contact lens wearers. Cont Lens Anterior Eye. 2017 Feb;40:15-24.

* Dumbleton, Kathy et al. "The impact of contemporary contact lenses on contact lens discontinuation." Eye & contact lens vol. 39:1 (2013): 93-9.

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are secreted into the tears, after which they can increase tear evaporation and affect tear film stability. It is important to note that these common OTC medications typically only cause dry eye issues when they are taken in excess of recommended doses.¹⁸

Narcotics, including hydrocodone and oxycodone, can also lead to DED due to their anticholinergic properties.⁸

Cannabis is becoming more widely prescribed, as well as used recreationally; it also should be an etiological consideration for the development of dry eye. It is believed that THC found in cannabis activates the cannabinoid CB1 receptors in the lacrimal gland, which may reduce tear secretion, leading to DED.¹⁸

Alcohol, too, is secreted into the tears, where it can cause disrupted tear concentration and shortened tear breakup time.⁵

Vitamins and Supplements

Most vitamins, including multivitamin supplements, are not associated with DED.¹⁹ However, some herbal products and other natural supplements are recognized to contribute to DED. The mechanisms of action are inconclusive, but are likely similar to the sicca effect in dry mouth. Niacin (vitamin B3), echinacea and kava are the three most common herbal products that contribute to DED.¹¹

Topical Medications

Although the focus of this article is systemic medication effects on the ocular surface, we would be remiss not to briefly touch on topical drugs as well. The investigation of DED induced by topical drugs is highly complicated, as patients prone to ocular surface disease (OSD) are typically excluded in clinical trials. Still, many topical medications and excipients have been considered to cause or aggravate DED. These classes of drugs include anti-glaucoma agents, antiviral agents, agents used to treat allergies, decongestants, miotics, mydriatics and cycloplegics, preservatives, anesthetics and NSAIDs. These drugs work at the

ocular surface through various mechanisms, ultimately causing toxic, allergic and/or immuno-inflammatory effects. As these medications are delivered directly to the ocular surface, they may also generate a chemical interaction with the lacrimal film, ultimately reducing aqueous secretion, disrupting the lipid layer or causing damage to goblet cells, corneal and conjunctival epithelium, corneal nerves or the eyelids.⁵

Clinically, it remains difficult to differentiate between iatrogenic effects and spontaneous changes in OSD. Most studied is the prevalence of OSD among patients treated long-term for glaucoma or ocular hypertension. Risk factors for developing DED in these patients are treatment duration, severity of glaucoma, higher intra-ocular pressure and the use of BAK-containing eye drops. Interestingly, the results of a recent survey showed that nearly 38% of glaucoma patients were using tear substitutes, more than half of which were preserved.⁵

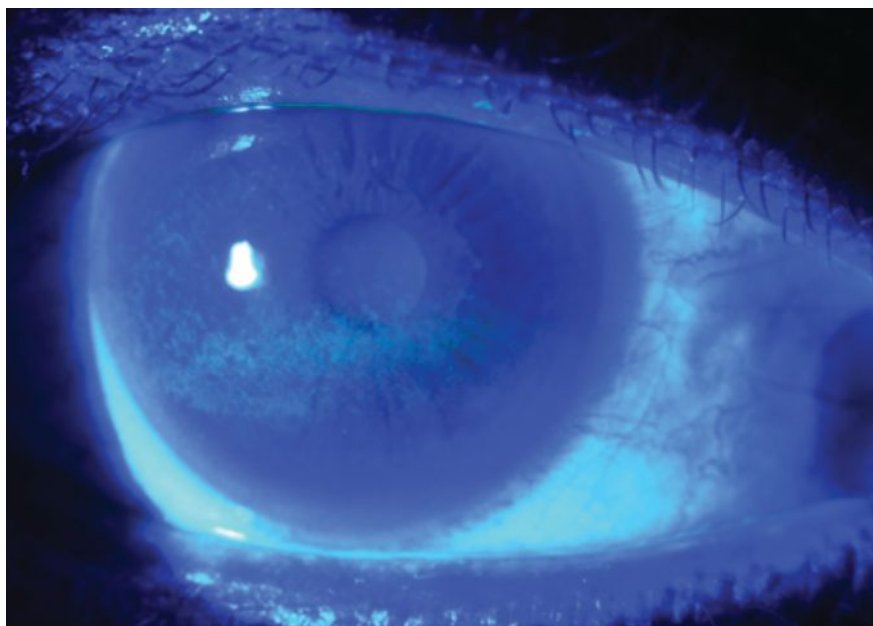
In diseases like glaucoma where the treatment is mandatory for a sight-threatening condition, discontinuation of therapy is not an option. It is recommended to reduce the number of preserved eye drops. Switching a patient

from a preserved to nonpreserved formulation or a different nonpreserved class of medication may significantly improve the appearance of the ocular surface and reduce patient symptoms. Additionally, implanted medication like Durysta or a multitude of surgical options can be considered to spare the ocular surface.⁵

Interdisciplinary Management and Treatment

Further complicating the assessment of iatrogenic dry eye is the issue of polypharmacy, which is defined as the use of five or more prescription drugs.⁴ This problem mainly affects older individuals and increases with age. Medication side effects have generally been reported to be three times greater in the older population, which suffers from DED the most.⁴ As age increases, drug clearance rates decrease, which may increase dry eye-related side effects.¹⁹ Furthermore, the interactions that many medications have with each other are difficult to predict and this becomes significantly more complex with the addition of each new medication.⁴

The underlying disease process should also be a consideration for dry eye symptoms. It is often difficult



Punctate epithelial erosions in a dry eye patient as revealed by fluorescein dye.

Photo: W.A. Buile, OD

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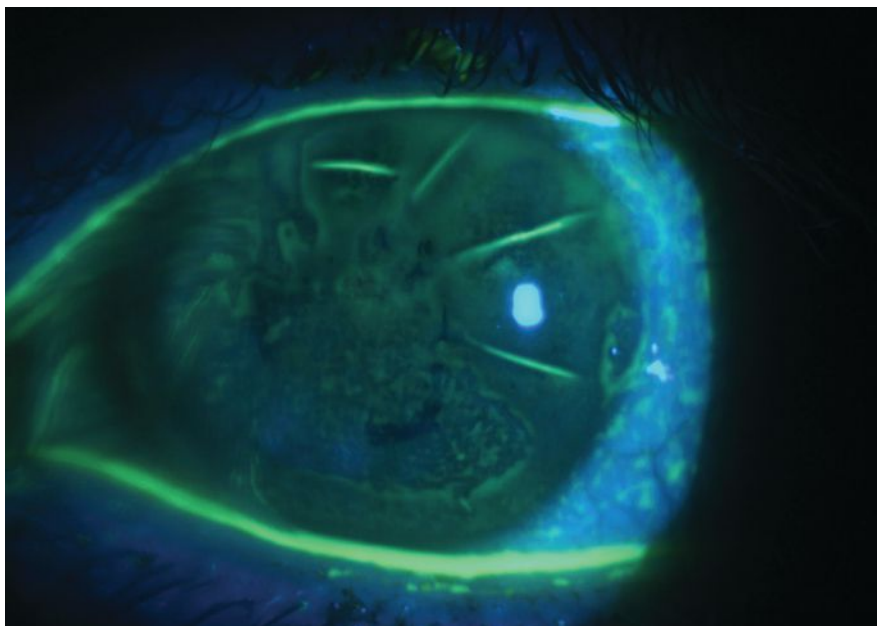


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Photo: Irene Frantzis, OD



Diffuse corneal staining with fluorescein in a patient with severe dry eye and a history of radial keratotomy.

to conclude whether DED is drug-induced or disease-induced. Despite the complexity and incomplete data, sufficient information is available to show that medication-induced DED is likely underestimated. A population-based study of 2,481 individuals between the ages of 64 and 84 estimated that 62% of dry eye cases in the elderly were caused by systemic medications, rather than the comorbid conditions themselves.²¹

When it is suspected that systemic medications are a factor in a patient's DED, patient education is the first step. Depending on symptom severity and the medication class that is the suspected aggravator, it may be indicated to suggest an alternative medication that is known to have less side effects of DED. A more localized drug administration method can also be recommended when possible.⁷ For example, an oral antihistamine regimen can be switched to an antihistamine nasal spray. In these cases, an interdisciplinary and collaborative approach is essential. A patient's primary care provider and/or prescribing specialist should be contacted if a modification to systemic medication is suggested. While optometrists are encouraged to

consider a medication change, that is not always feasible. In scenarios when an alternative medication dose or discontinuation is not recommended, optometrists should treat the DED complications independently.

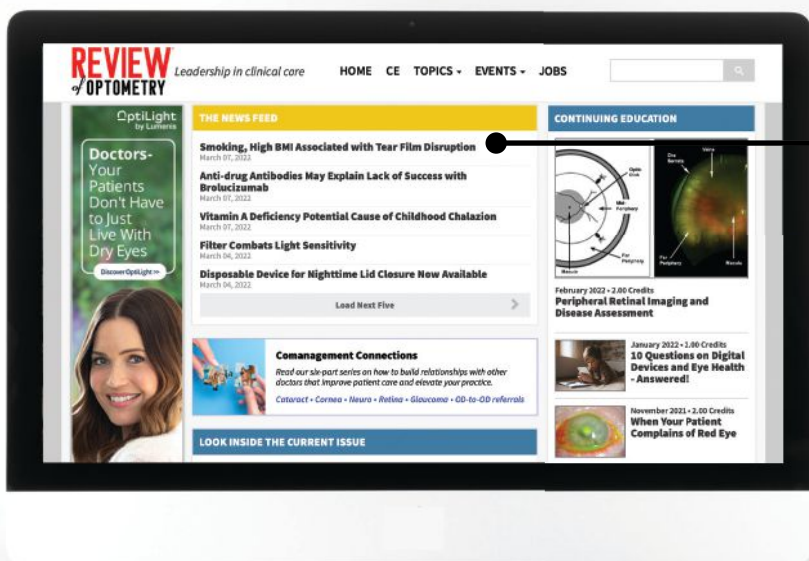
The DED treatment protocol will be similar no matter which systemic medication is the known or suspected culprit of a patient's dryness symptoms. Often in DED, combination therapy is required. The TFOS DEWS II Management and Therapy Report provides a step-wise approach to DED management.²² First-line treatment typically involves topical lubricants, including varying viscosity artificial tears, gels and ointments. Tears with less potent or no preservatives are preferred. Drugs with anti-inflammatory properties (*e.g.*, topical steroids, cyclosporine, lifitegrast) and oral doxycycline or azithromycin are other options. Additional treatment choices in more severe cases of DED include punctal plugs, scleral contact lenses and/or serum tears.²³

Ultimately, a person cannot choose their comorbidities, but it may be possible to reduce or alter medication therapy to reduce sicca symptoms. A detailed drug review is imperative as

providers continue to improve their approach to treatment of DED. The role systemic drugs play in DED is significantly underappreciated, but supporting data is still missing because of the difficulty in separating drug-induced from disease-induced DED.⁴ ■

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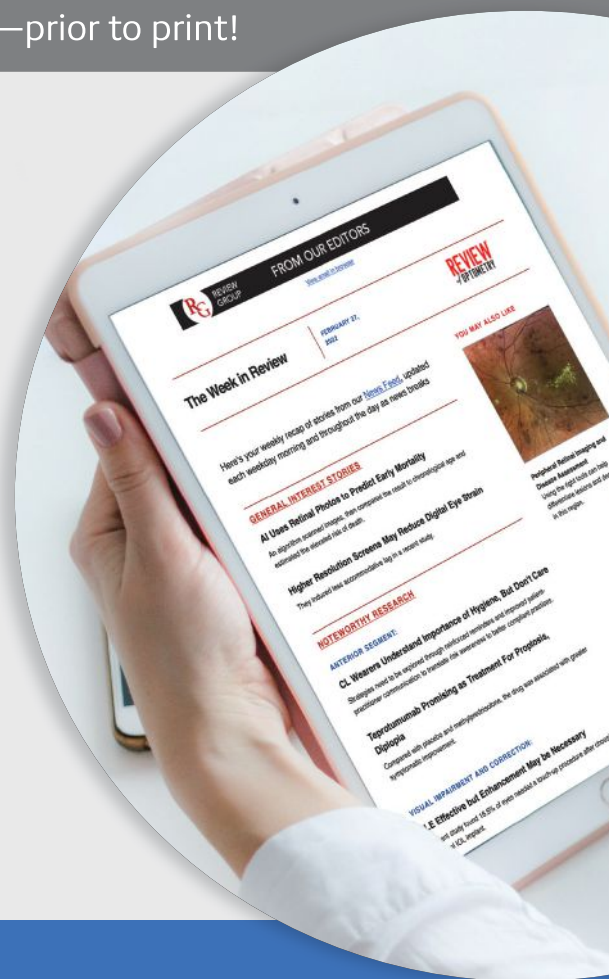
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CONJUNCTIVITIS: KNOW YOUR DIFFERENTIALS

The various forms of this condition display similar signs and symptoms, which can make a specific diagnosis challenging.



BY MARC BLOOMENSTEIN, OD
SCOTTSDALE, AZ

Commonly described as “pink eye,” conjunctivitis is a broad clinical term that includes a variety of infectious and noninfectious conditions. Typically it is characterized by inflammation and swelling of the conjunctival tissue, accompanied by engorgement of the blood vessels, ocular discharge and occasional pain.¹ More than 80% of all acute cases of conjunctivitis are reported to be diagnosed by non-ophthalmic clinicians, including internists, family medicine physicians, pediatricians and nurse practitioners, which makes it even more important for the ophthalmic community to be the final voice in the diagnosis.²

There are several ways to categorize conjunctivitis: by etiology, chronicity, severity and extent of involvement of the surrounding tissue. The etiology of conjunctivitis may be infectious or noninfectious, affecting people of any age, race or socioeconomic status. A

challenge for clinicians is differentiating other causes of “red eye” associated with severe sight- or life-threatening consequences. Since conjunctivitis may be associated with the involvement of the surrounding tissue, such as the eyelid margins and cornea, the diagnosis is not always straightforward.

Further adding to the importance of a timely diagnosis is the association between conjunctivitis and systemic conditions, including immune-related diseases (*e.g.*, Reiter’s, Stevens-Johnson syndrome and keratoconjunctivitis sicca in rheumatoid arthritis), nutritional deprivation (vitamin A deficiency) and congenital metabolic syndromes (Richner-Hanhart syndrome and porphyria).^{3,4} This article will delve into the different types of conjunctivitis to help optometrists narrow down the differentials and reach the correct diagnosis.

Diagnosing Conjunctivitis

This condition is characterized, but not limited to, conjunctival hyperemia, ocular discharge and, depending on

the etiology, discomfort and itching, with differing signs and symptoms. In a large meta-analysis, anisocoria and mild photophobia were significantly associated with non-conjunctivitis origins.⁵ The presence of these two signs could help diagnose 59% of cases, including those associated with anterior uveitis and keratitis.

Aside from the more common signs associated with conjunctivitis—discharge, conjunctival injection, mucus, grittiness, edema—a thorough history can guide the clinical diagnosis.⁶ A focused ocular history should include the following: onset and duration of symptoms, laterality, impairment of vision, presence of itch, contact lens wear, comorbidities such as infection, sinusitis and lymphadenopathy, previous episodes of conjunctivitis, systemic allergies and medication, as well as a history of exposure to chemical agents.

Associated symptom history, such as fever, malaise, fatigue and contact with individuals who have conjunctivitis, helps to define the differential diagnosis. SARS-CoV-2 should be included

About the author

Dr. Bloomenstein is the director of optometric service for the Schwartz Laser Eye Center in Scottsdale, AZ. Aside from contributing to numerous journals, he lectures frequently both nationally and internationally on various optometric topics. Dr. Bloomenstein has no financial interests pertaining to this article.

in any differential following the 2020 outbreak. Physical examination, including checking for palpable lymph nodes, especially in the periauricular and submandibular areas, is of great importance.

Whereas signs of redness and discharge are most commonly a cause of conjunctivitis, they do not differentiate the pathogen of origin.⁷ In one study, an accuracy rate of only 48% in making the correct diagnosis of adenoviral conjunctivitis was noted.⁸ Several other studies demonstrated that bacterial pathogens are only isolated in 50% of cases of suspected bacterial conjunctivitis.⁹ In addition, one study reported that up to 52% of presumed cases of viral conjunctivitis were culture-positive for bacteria.⁸

There are generalizations that can be used to differentiate conjunctivitis types. It is commonly believed that involvement of one eye followed by the second eye within 24 to 48 hours is indicative of bacterial infection, and that infection of the second eye after 48 hours should raise suspicion for a viral etiology.⁸ Further, a papillary conjunctival reaction or pseudomembranous conjunctivitis suggests a bacterial origin, whereas a follicular conjunctival reaction is more likely to indicate a viral etiology. However, caution should be exercised when using these signs to make a definitive diagnosis.

It is also loosely believed that an association between lack of itching

Photo: Christine Shindt, OD



VKC is a more severe form of conjunctivitis and is most likely allergic in origin.

and bacterial conjunctivitis, as well as recent upper respiratory tract infection and lymphadenopathy, favors a viral conjunctivitis: sinusitis. However, a 2003 meta-analysis failed to find any clinical studies correlating the signs and symptoms of conjunctivitis with its underlying etiology.¹⁰ Furthermore, a prospective study found the strongest predictors of bacterial conjunctivitis are bilateral matting of the eyelids, lack of itching and no previous history of conjunctivitis.¹¹ It was noted that the types of discharge (purulent, mucus or watery) or other symptoms were not specific to any particular class of conjunctivitis. In the case of herpes simplex virus, the lack of bilaterality can also be an indicator since the bilateral nature is uncommon.

Acute conjunctivitis of all causes is estimated to occur in six million Americans annually.¹² The highest rates are among children who are younger than seven years old, with the highest incidence occurring between birth and age four. Allergic conjunctivitis, affecting 15% to 40% of the population, is the most common type and is seen most often in the spring and summer. Acute bacterial conjunctivitis is the second most common, and its rates are highest from December to April.¹

Conjunctival cultures are generally reserved for cases of suspected infectious neonatal conjunctivitis, recurrent conjunctivitis, conjunctivitis recalcitrant to therapy, conjunctivitis presenting with severe purulent discharge and cases suspicious for gonococcal

Release Date: November 15, 2022

Expiration Date: November 15, 2025

Estimated Time to Complete Activity: two hours

Jointly provided by the Postgraduate Institute for Medicine (PIM) and Review Education Group

Educational Objectives: After completing this activity, the participant should be better able to:

- Recognize the key features of different types of conjunctivitis.
- Accurately diagnose the specific cause of conjunctivitis.
- Differentiate between allergic, viral and bacterial conjunctivitis.
- Educate their patients on the underlying cause of their condition.

Target Audience: This activity is intended for optometrists engaged in conjunctivitis management.

Accreditation Statement: In support of improving patient care, this activity has been planned and implemented by PIM and the Review Education Group. PIM is jointly accredited by the Accreditation Council for Continuing Medical Education, the Accreditation Council



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Viral conjunctivitis is often an acute, contagious conjunctival infection related to an infection of the upper respiratory tract or an adenovirus. Symptoms, which are usually limited to one eye at a time, include irritation, photophobia and watery discharge.

or chlamydial infection.¹³ Although primary studies from in-office rapid antigen testing for adenoviruses report 89% sensitivity and up to 94% specificity, the results of more recent studies point toward a high specificity but only moderate sensitivity ranging from 40% to 50%.^{13,14} Accordingly, it may be suggested that negative test results should be confirmed by real-time PCR owing to the test's suboptimal sensitivity.

Viral Conjunctivitis

This is the most common cause of infectious conjunctivitis, causing up to 80% of all acute cases, with many misdiagnosed as bacterial conjunctivitis.¹⁵ Between 65% and 90% of viral conjunctivitis cases are caused by adenoviruses, and they produce the three most common presentations associated with this conjunctivitis: follicular conjunctivitis, pharyngoconjunctival fever and epidemic keratoconjunctivitis.^{16,17} Let's review each in turn.

Follicular conjunctivitis is the mildest form of a viral conjunctival infection. It has an acute onset, initially unilateral with the second eye becoming involved after about a week. It presents with a watery discharge, hyperemia, follicular reaction and a preauricular lymphadenopathy on the affected side. Most cases resolve spontaneously.¹⁸

The most common form of adenovirus infection in children is *pharyngoconjunctival fever* caused by HAdV types 3, 4 and 7.¹⁹⁻²¹ This condition is usually characterized by the presence of fever, pharyngitis, periauricular lymphadenopathy and acute follicular conjunctivitis. Ocular findings include edema, hyperemia and petechial hemorrhages of the conjunctiva.²⁰ This condition is self-limited, often resolving spontaneously in two to three weeks without any treatment. Patients should be educated as to the contagious nature of these viruses, use proper hygiene and avoid direct contact during the contagious period.

The most severe ocular manifestation of adenoviral infection is *epidemic keratoconjunctivitis* (EKC), affecting both the conjunctiva and cornea, with the potential to leave long-lasting, permanent ocular surface changes and visual disturbances. Ocular manifestations of EKC include conjunctival discharge, follicular conjunctivitis, corneal subepithelial infiltrates (SEIs), corneal scarring, conjunctival membranes and pseudomembranes and symblepharon formation. Pseudomembranes, which are sheets of fibrin-rich exudates without blood or lymphatic vessels, may be encountered in the tarsal conjunctiva of the EKC patient.²² Depending on the

intensity of inflammation, true conjunctival membranes may also form in EKC. True membranes, once formed, can lead to the development of subepithelial fibrosis and symblepharon.²³

Timely diagnosis of these adenoviruses is critical, as the replication of the virus in the corneal epithelium may cause superficial punctate keratopathy, followed by focal areas of epithelial opacities.²⁴ Focal SEI in the anterior stroma of the cornea appears approximately seven to 10 days following the initial involvement of the eye with EKC.²⁵ These opacities may persist for years, and they can be associated with visual disturbance, photophobia and astigmatism. The incidence of SEI formation in EKC has been reported to vary from 49% to 80%.²⁶ It is believed that an immunologic reaction to the replicating adenoviruses in the anterior stromal keratocytes leads to the formation of SEIs. In fact, the recurrence of SEIs following discontinuation of steroids is a strong indicator of this theory.²⁷

Adenovirus conjunctivitis is very contagious, with reports showing it may be transmitted up to 50% of the time.²⁸ The virus is most commonly spread from the hands. As many as 46% of individuals with viral conjunctivitis had positive viral culture grown from their hands, according to one study. The virus may also spread through office equipment, swimming pools or sharing personal items.²⁹ The incubation period for the adenovirus is approximately five to 12 days, while the infected individual can transmit the disease for up to 14 days from the time they are infected.²⁸ With such high transmission rates, the use of gloves and hand washing is imperative within the office.

There is no single effective treatment modality for viral conjunctivitis; however, palliative treatment is recommended.³⁰ Off-label topical ganciclovir has been used against EKC, showing potential against specific adenovirus serotypes *in vitro*.⁹ One study compared the effects of ganciclovir 0.15% ophthalmic ointment with preservative-

free artificial tears for 18 patients with adenovirus keratoconjunctivitis.³¹ The ganciclovir group demonstrated resolution of the conjunctivitis in 7.7 days as opposed to 18.5 days for the artificial tear group. Additionally, topical antibiotics do not play a role in treating viral conjunctivitis. Most potentially obscure the clinical picture by inducing ocular surface toxicity, increasing bacterial resistance and spreading the disease to the contralateral eye by cross-contamination through the infected bottles.^{8,32}

A monotherapy against viral conjunctivitis with povidone-iodine 2%, a broad-spectrum antimicrobial with high microbial kill rates, has been investigated. Researchers found that the topical administration of povidone-iodine 2% four times a day for one week led to complete resolution of the disease in three-quarters of the study eyes.³³ Varying concentrations of povidone-iodine/dexamethasone suspension have also been used, and the results suggest that the combination therapies reduce patient symptoms and eradicate the virus effectively.³⁴ Additionally, the use of cyclosporin or cyclosporine A eye drops has been suggested to help treat corneal infiltrates.³⁵

Although not as common as adenoviruses, herpes simplex is estimated to cause 1.3% to 4.8% of all cases of viral conjunctivitis.³⁶ The zoster virus has also been shown to induce conjunctival involvement, rarely with corneal involvement.

Acute hemorrhagic conjunctivitis is another extremely contagious virus. It manifests through foreign body sensation, profuse tearing, eyelid edema, dilatation of conjunctival vessels, chemosis and the hallmark sign of subconjunctival hemorrhage.³⁷ Be wary of the monocular viral infection. Since—as previously discussed—viral infections tend to be bilateral, a unilateral presentation should elicit further testing in-clinic.

Bacterial Conjunctivitis

Among adults, this condition is less common than viral conjunctivitis. However, in children it is encountered

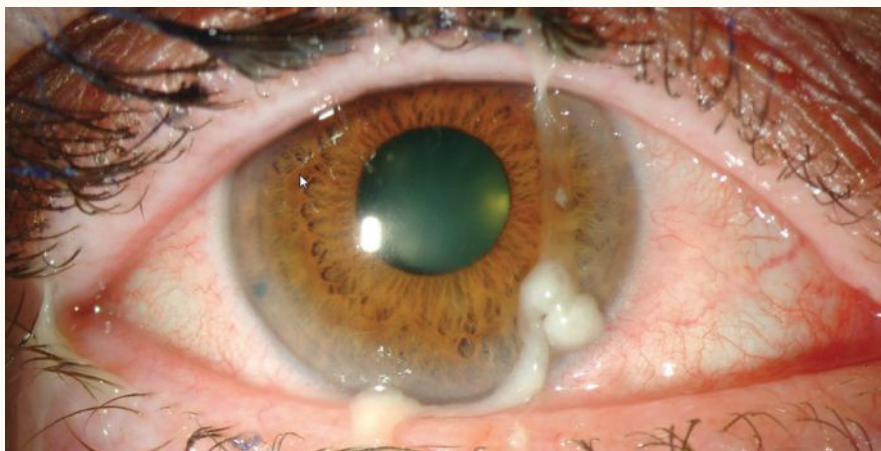


Photo: Christine Strudt, OD

Bacterial conjunctivitis is often a byproduct of the natural flora of the individual and is most commonly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus*.

more frequently, specifically in the form of *Haemophilus influenzae*.³⁸ Bacterial conjunctivitis can result from either direct contact with infected individuals or from abnormal proliferation of the native conjunctival flora.

Acute bacterial conjunctivitis is most often caused by *Staphylococcus* species, *Haemophilus influenzae*, *Streptococcus* species, *Moraxella catarrhalis* and gram-negative intestinal bacteria.³⁹ In more than 60% of cases, spontaneous resolution occurs within one to two weeks, and serious complications are extremely rare.^{40,41} However, the presence of a large population of bacteria on the conjunctiva exposes the patient to a higher risk of keratitis, particularly in conditions associated with corneal epithelial defects.³⁹

Topical antibiotics have long been the gold standard in treatment for bacterial conjunctivitis. Although this approach reduces the duration of the disease, no difference in the outcome has been reported between the treatment and placebo groups. In a meta-analysis consisting of 3,673 patients from 11 randomized clinical trials, topical antibiotic treatment increased the rate of clinical improvement by only 10% compared with placebo.⁴² Furthermore, there is growing resistance to antibiotics and methicillin-resistant *S. aureus* and total resistance to all β -lactam antimicrobials.⁴³ Suspected cases of MRSA/MRSE need to be treated with

fortified vancomycin eye drops or ointments, which are obtainable through a specialty pharmacy that can compound these medications.⁴⁴

Chlamydial Conjunctivitis

A variety of ocular surface infections can be caused by *Chlamydia trachomatis* including trachoma, neonatal conjunctivitis and inclusion conjunctivitis. Inclusion conjunctivitis is reported to cause 1.8% to 5.6% of all cases of acute conjunctivitis, where the majority of cases are unilateral and have concurrent genital infection.^{45,46} Patients often present with mild mucopurulent discharge and follicular conjunctivitis persisting for weeks to months.³⁷ Up to 54% of men and 74% of women are reported to have simultaneous genital infection.⁴⁷ Treatment with systemic antibiotics such as oral azithromycin and doxycycline is efficacious, while the addition of topical antibiotics is not beneficial.

Trachoma is the leading cause of infectious blindness in the world, affecting 40 million individuals worldwide. This infection is prevalent in areas with poor hygiene. Although mucopurulent discharge is the initial presenting sign, in the later stages, scarring of the eyelids, conjunctiva and cornea may lead to loss of vision. Treatment consists of topical antibiotic ointments, such as tetracycline and erythromycin, in coordination with a systemic antibiotic.⁴⁸



Photo: Paul M. Kampecki, OD, and Diana L. Sheehy, OD

Adult inclusion conjunctivitis is caused by *Chlamydia trachomatis* and has an incubation period of two to 19 days. Most patients have a unilateral mucopurulent discharge, as well as a follicular and hyperemic tarsal conjunctiva response.

Gonococcal Conjunctivitis

Typically viewed as a condition affecting neonates, gonococcal conjunctivitis affects other age groups as well. *Neisseria gonorrhoeae* is a common cause of hyperacute conjunctivitis in neonates and sexually active adults.⁴⁹ Ocular infection with *N. gonorrhoeae* is associated with a high prevalence of corneal perforation.³⁹ Gonococcal conjunctivitis should be considered the causative agent in neonates who present with conjunctivitis in days two to five after delivery.⁵⁰ In both neonatal and non-neonatal populations, conjunctival injection and chemosis, along with copious mucopurulent discharge and a tender globe with periauricular lymphadenopathy, may also be associated with this type of conjunctivitis.⁵⁰ The suggested treatment for neonates includes systemic management to eradicate the infection.

Allergic Conjunctivitis

Allergy diagnoses have dramatically increased in the last decades secondary to advances in genetics, increased air pollution, foliage, pets and early childhood exposure.⁵¹ A study classified ocular allergic conditions into three main categories: *IgE-mediated reactions*, including seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), *combined IgE and non-IgE-mediated reactions*, including vernal keratoconjunctivitis (VKC) and

atopic keratoconjunctivitis (AKC), and *non-IgE-mediated reactions*, including giant papillary conjunctivitis (GPC) and contact dermatitis.

SAC and PAC

These forms are considered the most prevalent allergic ocular conditions, affecting 15% to 20% of the population.⁵² The pathogenesis is predominantly an IgE-mediated hypersensitivity reaction, and allergen-specific IgE antibodies are found in almost all cases of SAC and PAC.⁵² Activation of mast cells contributes to increased levels of histamine, prostaglandins and leukotrienes in the tear film. This early phase lasts 20 to 30 minutes clinically.⁹ The chemokine release initiates recruitment of inflammatory cells into the conjunctival mucosa, which leads to the late-phase allergic reaction characterized by infiltration of inflammatory cells a few hours after the initial mast cell activation.⁵³

The ocular manifestations of SAC occur predominantly during the spring and summer months when pollens from the trees and plants are released into the air. PAC, on the other hand, can occur throughout the year with exposure to more common allergens such as animal hair, mites and feathers.⁵⁴ Clinical signs and symptoms are similar in SAC and PAC and include eye itching, burning and tearing. A distinguishing feature is the rare involvement of the cornea.¹⁰

VKC

This condition is known as the disease of young males living in warmer climates.⁵⁵ Although VKC is frequently diagnosed in children, adults can also be affected as well.⁵⁶ A mixture of IgE and non-IgE reactions in response to nonspecific stimuli, such as wind, dust and sunlight, is often elucidated in this condition. A strong link between VKC and other autoimmune disorders, including atopy, has been suggested.

Conjunctival injection, profuse tearing, severe itching and photophobia are the main clinical signs and symptoms that are associated with VKC. There are three clinical forms of VKC: *limbal* (limbal papillary reaction and gelatinous thickening of the limbus and Horner-Trantas dots at the superior limbus), *palpebral* (giant cobblestone papillae) and *mixed palpebral and limbal* involvement.⁵⁴

The corneal pathology that is seen in VKC is attributed to the mechanical trauma from the tarsal conjunctival papillae and the inflammatory sequelae of cytokines. In up to 6% of patients, corneal ulcers and plaques develop, leading to exacerbation of clinical symptoms and decreased vision.⁵⁷ Keratoconus is also highly associated with VKC, affecting nearly 15% of patients with this condition.⁵⁸

AKC

Characterized by chronic allergic disease of the eyelid, cornea and conjunctiva, AKC is considered the ocular component of atopic dermatitis (AD). Roughly 95% of patients with AKC have concomitant AD.^{9,12} However, less than 50% with AD have involvement of the ocular tissue.⁵⁹ Conjunctival cytokines, as well as inflammatory cells, infiltrate the conjunctival tissues in AKC, causing constant remodeling of the ocular surface connective tissue, which leads to mucus metaplasia, scar formation and corneal neovascularization.⁶⁰

Clinical manifestation of AKC includes epiphora, itching, redness and decreased vision. Presentation is often bilateral; however, unilateral disease

has been reported.⁶¹ The eyelid skin may be edematous with a sandpaper-like texture. Conjunctival injection and chemosis range from mild to severe, and conjunctival scarring is common.¹² Trantas dots and giant papillae may or may not be present. In contrast to VKC, AKC is associated with conjunctival fibrosis and corneal vascularization and opacities. Furthermore “atopic cataracts” are seen at a relatively young age. Shield-like cataracts, as well as nuclear, cortical and even posterior subcapsular cataracts, may also occur. Interestingly, nearly 50% of AKC patients test negative for common allergens.⁹

GPC

Similar to VKC, this condition is characterized by papillary hypertrophy of the superior tarsal conjunctiva.⁶² Although GPC is primarily considered a complication of contact lens usage, this condition has also been reported in association with corneal foreign bodies, filtering blebs, ocular prostheses, exposed sutures, limbal dermoids and tissue adhesives.⁶³ The classic signs of GPC consist of excessive mucus secretion associated with decreased contact lens tolerance. Mechanical injuries due to contact lens wear and inflammatory reactions secondary to surface proteins of the lens can contribute to chronic inflammatory damage of the ocular surface.⁶⁴

Allergy Treatment

Avoidance of allergens is the mainstay of treatment for many forms of allergies, including allergic conjunctivitis. Chilled artificial tears provide a barrier function, diluting various allergens and inflammatory mediators. Treatment options for allergic conjunctivitis include lubricating eye drops, antihistamines and mast cell stabilizers.⁶⁵

Many studies have demonstrated the superiority of topical antihistamines and mast cell stabilizers compared with placebo in alleviating the symptoms of allergic conjunctivitis.⁶⁶ There are several eyedrop preparations with dual action, antihistamine and mast cell-sta-



Photo: Christine Sindi, OD

Allergic conjunctivitis is due to a type one hypersensitivity reaction to a specific antigen.

bilizing effects, providing simultaneous histamine receptor antagonist effects, stabilizing mast cell membranes and modifying the action of eosinophils.⁶⁷ Most ocular allergy patients concomitantly suffer from systemic symptoms and although second-generation oral antihistamines are preferred due to their fewer adverse systemic side effects, they induce ocular drying.⁶⁸

Steroids are the most potent medications used in allergic conjunctivitis and are effective in treating both acute and chronic presentations.⁶⁹ Yet, as with any medication, there are limitations with steroid use, and a short course of steroid therapy may be prudent. A low-dose, non-ketone-based steroid should be considered for the long term. Non-steroidal anti-inflammatory drugs can also be added to the treatment regimen as well as other steroid-sparing agents such as cyclosporin or cyclosporine A and tacrolimus in treating severe and chronic forms of ocular allergies.

Systemic Disease Association

Conjunctivitis may be the initial presentation for many systemic diseases. These can include reactive arthritis, manifesting as conjunctival hyperemia with purulent discharge (an essential component of Reiter’s triad); rosacea, including a follicular and papillary reaction, cicatrization of the conjunctiva and scarring secondary to entropion and trichiasis; and graft-vs.-host disease

with conjunctival involvement indicating a more severe systemic involvement and poor prognosis.⁷⁰⁻⁷² Ocular cicatricial pemphigoid, though rare, can induce loss of conjunctival goblet cells and drying of the ocular surface.⁷³ Another example is Stevens-Johnson syndrome, which varies from conjunctival hyperemia to near-complete sloughing of palpebral conjunctiva and lid margins with acute ocular involvement reported in up to 88% of cases.⁷⁴

Toxic Conjunctivitis

Long-term use of topical eye medications may induce ocular surface changes, including dry eye, conjunctival inflammation, ocular surface fibrosis and scarring.⁷⁵ There is a high ocular morbidity seen in glaucoma patients as well as those who have undergone glaucoma surgery. Subclinical infiltration of the conjunctival epithelium and substantia propria by inflammatory cells has also been reported.⁷⁶ Literature published during the past decade has pointed to the deleterious effects of benzalkonium chloride, which is often used as a preservative in eye drops, on the ocular surface.⁷⁷ Limiting exposure to preservatives may diminish the toxic side effects of drops; this will likely lead to higher patient compliance and result in more favorable clinical outcomes, especially in those who need to be on glaucoma medications.

Takeaways

Conjunctivitis encompasses a wide range of diseases occurring worldwide. It rarely causes permanent vision loss, but its impact on patients' quality of life can be considerable. Our clinical duty is to properly diagnose and, when necessary, treat this condition, whatever its origin, with a targeted approach. ■

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OPTOMETRIC STUDY CENTER QUIZ

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1. Which percentage of bacterial conjunctivitis spontaneously resolves within one to two weeks?
 - a. 30%.
 - b. 40%.
 - c. 50%.
 - d. 60%.
2. What is the most common overall infectious conjunctivitis in adults?
 - a. Allergic.
 - b. Viral.
 - c. Bacterial.
 - d. Toxic.
3. A prospective study found which of the following to be the strongest predictor of bacterial conjunctivitis?
 - a. Mattering of the lids.
 - b. Lack of itching.
 - c. No previous history of conjunctivitis.
 - d. All of the above.
4. Which of the following would most likely be diagnosed during the summer months?
 - a. Bacterial.
 - b. Toxic.
 - c. Allergic.
 - d. Viral.
5. A patient has had a chemotic watery left eye for over three weeks. Which of the following would be the most likely diagnosis?
 - a. Chlamydial conjunctivitis.
 - b. Herpes simplex virus.
 - c. EKC.
 - d. Allergic conjunctivitis.
6. Conjunctivitis has been associated with all of the following systemic conditions except which?
 - a. Diabetes.
 - b. Reiter's.
 - c. Vitamin A deficiency.
 - d. Porphyria.
7. In a meta-analysis, mild photophobia and what were found in 59% of cases that were not conjunctivitis?
 - a. Epiphora.
 - b. Stringy discharge.
 - c. Munson's sign.
 - d. Anisocoria.
8. Which of the following is considered to be a condition that affects the neonates?
 - a. Allergic conjunctivitis.
 - b. Gonococcal conjunctivitis.
 - c. Herpes zoster conjunctivitis.
 - d. EKC.
9. Which of the following is known as the disease of young males and is strongly linked to atopy?
 - a. Gonococcal conjunctivitis.
 - b. GPC.
 - c. VKC.
 - d. SAC.
10. Suspected cases of MRSA should be treated with which of the following?
 - a. Besivance.
 - b. Fortified vancomycin.
 - c. Ciloxan.
 - d. Fortified dexamethasone.
11. A patient presents with foreign body sensation, profuse tearing, chemosis and profound subconjunctival hemorrhaging. What is your initial diagnosis?
 - a. EKC.
 - b. GPC.
 - c. VKC.
 - d. AKC.
12. In a meta-analysis of 3,673 bacterial conjunctivitis patients, how often did a topical antibiotic demonstrate clinical improvement?
 - a. 10%.
 - b. 20%.
 - c. 40%.
 - d. 60%.
13. At 15% to 20% of the population, which of the following is considered to be the most prevalent conjunctivitis?
 - a. Viral.
 - b. Allergic.
 - c. Bacterial.
 - d. Herpes simplex.
14. Which of the following is not a treatment for SAC?
 - a. Steroids.
 - b. Artificial tears.
 - c. Topical mast cell stabilizers.
 - d. Oral antihistamines.
15. Which of the following signs would you not expect to see in a case of toxic conjunctivitis?
 - a. Anisocoria.
 - b. Keratoconjunctivitis sicca.
 - c. Inflammation.
 - d. Scarring.
16. When diagnosing conjunctivitis, which of the following ocular tissues could be associated with this condition?
 - a. Lids.
 - b. Cornea.
 - c. Conjunctiva.
 - d. All of the above.
17. The existence of a palpable lymph node is most likely associated with which of the following?
 - a. VKC.
 - b. GPC.
 - c. Allergic conjunctivitis.
 - d. AKC.
18. The presence of a papillary reaction and pseudomembrane strongly suggests which diagnosis?
 - a. Viral.
 - b. Allergic.
 - c. Toxic.
 - d. Bacterial.
19. A patient has conjunctivitis with no itch in the right eye, and 96 hours later, they develop it in their left eye. This suggests which diagnosis?
 - a. Viral.
 - b. Allergic.
 - c. Toxic.
 - d. Bacterial.
20. What percent of acute conjunctivitis cases are diagnosed by eyecare clinicians?
 - a. 100%.
 - b. 60%.
 - c. 40%.
 - d. 20%.

Examination Answer Sheet

Conjunctivitis: Know Your Differentials

Valid for credit through November 15, 2025

Online: This exam can be taken online at revieweducationgroup.com. Upon passing the exam, you can view your results immediately and download a real-time CE certificate. You can also view your test history at any time from the website.

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

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Answers to CE exam:

1. (A) (B) (C) (D)
2. (A) (B) (C) (D)
3. (A) (B) (C) (D)
4. (A) (B) (C) (D)
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18. (A) (B) (C) (D)
19. (A) (B) (C) (D)
20. (A) (B) (C) (D)

Post-activity evaluation questions:

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

21. Recognize the key features of different types of conjunctivitis. ① ② ③ ④ ⑤
22. Accurately diagnose the specific cause of conjunctivitis. ① ② ③ ④ ⑤
23. Differentiate between allergic, viral and bacterial conjunctivitis. ① ② ③ ④ ⑤
24. Educate their patients on the underlying cause of their condition. ① ② ③ ④ ⑤
25. Based upon your participation in this activity, do you intend to change your practice behavior? (Choose only one of the following options.)
 - (A) I do plan to implement changes in my practice based on the information presented.
 - (B) My current practice has been reinforced by the information presented.
 - (C) I need more information before I will change my practice.
26. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit? (please use a number):
27. If you plan to change your practice behavior, what type of changes do you plan to implement? (Check all that apply.)

(A) Apply latest guidelines	(D) Change in current practice for referral	(G) More active monitoring and counseling
(B) Change in diagnostic methods	(E) Change in vision correction offerings	(H) Other, please specify: _____
(C) Choice of management approach	(F) Change in differential diagnosis	
28. How confident are you that you will be able to make your intended changes?
 - (A) Very confident
 - (B) Somewhat confident
 - (C) Unsure
 - (D) Not confident
29. Which of the following do you anticipate will be the primary barrier to implementing these changes?

(A) Formulary restrictions	(D) Insurance/financial issues	(G) Patient adherence/compliance
(B) Time constraints	(E) Lack of interprofessional team support	(H) Other, please specify: _____
(C) System constraints	(F) Treatment related adverse events	
30. Additional comments on this course: _____

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Rate the quality of the material provided:

1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree

31. The content was evidence-based.

① ② ③ ④ ⑤

32. The content was balanced and free of bias.

① ② ③ ④ ⑤

33. The presentation was clear and effective.

① ② ③ ④ ⑤

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

Signature _____ Date _____ Lesson 123319 RO-OSC-1122

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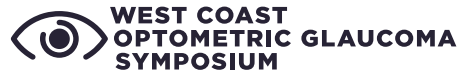
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EDITED BY JOSEPH P. SHOVLIN, OD

Picking a Procedure

Previous surgeries can complicate what operation works best for patients with endothelial dysfunction.

Q I have a patient who needs a lamellar graft for endothelial dysfunction but has previously had a vitrectomy for a retinal detachment. Can this patient have a Descemet's membrane endothelial keratoplasty (DMEK) procedure to restore corneal integrity or should a different form of lamellar surgery be used?

A Descemet's stripping automated endothelial keratoplasty (DSAEK) and DMEK have improved nearly every aspect of the immunologic and optical impact of penetrating keratoplasty for patients with endothelial disease. "Despite these improvements, both present unique challenges, particularly intraoperatively and in the early postoperative period. Prior ophthalmic surgery in some cases can add dramatic complexity to the case," says Aaron Bronner, OD, of

Pacific Cataract and Laser Institute in Boise, ID.

Of particular concern are previous vitrectomy, filtering tubes or trabeculectomies, large surgical iridectomies or any procedure or trauma resulting in a significant compromise to the zonulo-capsular complex and aphakia.

Background

Understanding how these surgeries potentially complicate DSAEK or DMEK requires a bit of understanding about the surgical process of each. Dr. Bronner explains that in both transplant types, the central host Descemet's membrane and endothelium is scored and carefully removed. The graft is then introduced into the anterior chamber. In DSAEK, the graft generally unfolds easily with injection of a balanced salt solution.

With DMEK, the graft is scrolled, and getting it to un-scroll is a bit of a trick, as the surgeon can't simply grab it and unroll it—excessive direct touch will often cause the graft endothelium to fail. Instead, the surgeon relies on percussive waves and balanced salt solution flow through the anterior chamber to get the graft to un-scroll. The surgeon facilitates this by somewhat shallowing the anterior chamber, as surface tension interactions between both the host cornea and iris with the graft assist with its unrolling.

Once the graft is in position, an air or air/gas mix is injected into the anterior chamber and the eye is pressurized (and chamber deepened) for a period in surgery and the patient is observed.

After some time, the eye is depressurized through a bubble (of variable size and make-up, depending on the surgery) is left in place, Dr. Bronner describes. The patient is sent home with positioning restrictions to remain supine for much of the following days. This allows the



In this photo sequence, cornea surgeon Jim Guzek, MD, is unrolling a DMEK graft. The graft is stained with Trypan Blue to aid visualization of the very thin tissue. Through circulating BSS and creating percussive waves through the cornea, with the aid of surface tension interactions of the graft, host cornea and iris, he is able to get the tightly scrolled transplant to unroll without touching it.

About Dr. Shovlin

Dr. Shovlin, a senior optometrist at Northeastern Eye Institute in Scranton, PA, is a fellow and past president of the American Academy of Optometry and a clinical editor of *Review of Optometry* and *Review of Cornea & Contact Lenses*. He consults for Kala, Aerie, AbbVie, Novartis, Hubble and Bausch + Lomb and is on the medical advisory panel for Lentechs.

bubble to press the graft into place and, if the transplanted endothelium is viable, will allow the graft to remain in position as the bubble re-absorbs.

Complications

“Vitreotomy can create two particular issues for DMEK. First, the anterior chamber and vitreal cavity are no longer separate pressure systems; second, the ability to shallow the anterior chamber to aid in the unrolling of the graft is inhibited. This problem is specific to DMEK and does not apply to DSAEK. Secondly, if the patient also has a compromise to the capsule or zonules, the air/gas bubble can escape posteriorly and may remain stuck behind the intraocular lens.

Without a predictable air/gas bubble tamponade, the graft is likely to detach. This can be a problem for both DSAEK and DMEK. “Not all vitrectomized eyes have compromised capsular/zonular integrity, so this issue varies by individual,” Dr. Bronner notes. “Large superior surgical

iridectomies and scleral fixated IOLs may also complicate these transplants due to posterior migration of the air bubble,” he adds.

Filtering surgeries create issues with the ability to pressurize the eye after placement of the graft. If the eye can’t be pressurized appropriately, it is much more difficult to get the graft to adhere prior to sending the patient home. Further, eyes with glaucoma severe enough to justify filtering surgery may not be good candidates for DSAEK or DMEK because of attempts that will be made to pressurize the eye and the impact that may have on their remaining retinal nerve fiber layer.

According to Dr. Bronner, aphakia complicates DSAEK and DMEK. Though you can imagine getting a bubble to stay in the anterior chamber may be difficult in a patient with aphakia, usually these patients have already had vitrectomies, so the entire eye can often be filled with gas/air. Instead, the primary issue is not being

able to easily shallow the chamber (as with simple vitrectomy) and the potential for the transplant dropping to the retina intraoperatively.

Descemet’s stripping only may be used to avoid these issues, however, the surgery is niche. Descemet’s stripping only is limited to patients who have endothelial disease from Fuchs’ dystrophy (no other source of endothelial decompensation can be treated with this surgery), and it tends to work best in those who primarily have central involvement, so isn’t an option in many cases of endothelial decompensation.

“None of these postoperative states create problems that are entirely insurmountable, but cases like this may exceed the comfort or ability of community cornea specialists who may perform only a couple transplants a month,” concludes Dr. Bronner. “Centers that specialize in transplants specifically may be better suited to tackle cases that are anticipated to be challenging.” ■

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Sweat the Small Stuff

Even though they may not look like much initially, open globe injuries may have significant visual consequences if mismanaged.

A 50-year-old female presented to the ophthalmic emergency department for foreign body sensation and pain OD for four days. She said her symptoms started after a cabinetry unit she had been holding slipped and forcefully hit her in the eye. She reported immediate pain and blurred vision. Since the accident, her pain and vision had improved; however, she was still experiencing persistent photophobia and headaches, which ultimately prompted her to seek care.



This gross slit lamp photo reveals nasal conjunctival injection and a faint corneal opacity nasal to the center. There is also mild haze visible in the lens of the eye, where a focal cataract is present.

Case

On examination, her vision was 20/150 (pinhole 20/40) OD and 20/20 OS. Her intraocular pressures were 16mm Hg OD and 17mm Hg OS. The pupillary exam revealed pupils that were equal in size and no afferent pupillary defect. Her extraocular motilities were normal. Slit lamp examination revealed mild nasal injection in the right eye with a 4mm linear full-thickness corneal laceration nasally. The anterior chamber of the right eye had 1+ cell and 1-2+

pigment. There was a focal anterior cataract nasocentrally. The posterior segment exam was unremarkable, and no evidence of vitritis, intraocular foreign body or retinal damage was seen. The left eye exam was unremarkable.

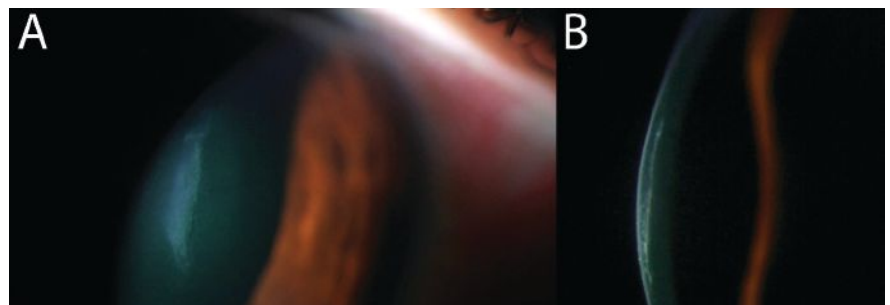
Given the full-thickness corneal laceration, signifying an open globe injury, it was important to conduct additional testing to fully understand the integrity of the globe. A Seidel test was completed by anesthetizing the eye and applying a wetted fluorescein strip directly over the wound under a blue light filter. There was no fluid emitting from the wound. Next, the test was repeated while applying gentle pressure to the globe to assess the wound's stability under mild stress, which could be induced if the patient accidentally rubbed the eye or when IOP was checked. The wound did not leak with provocation, signifying it had self-sealed. Corneal cross-section images revealed the beveled nature of the wound, likely explaining why the laceration did not leak.

In any case of open globe injury, a thorough examination of the eye and periocular structures is critical. In cases

of polytrauma, blunt facial trauma or intraocular foreign body, computed tomography may be ideal.¹ In this case, the posterior segment view was clear, and retinal trauma and intraocular foreign body could be ruled out. In cases that present with intraocular hemorrhage—either a hyphema and/or vitreous hemorrhage—and an obscured fundus view, it may be beneficial to obtain ocular ultrasonography to evaluate the interior of the eye.² However, this should only be done by a provider who is very experienced using the technique, as further compression on the globe could cause other complications such as extrusion of intraocular contents or suprachoroidal hemorrhage.¹

Considerations

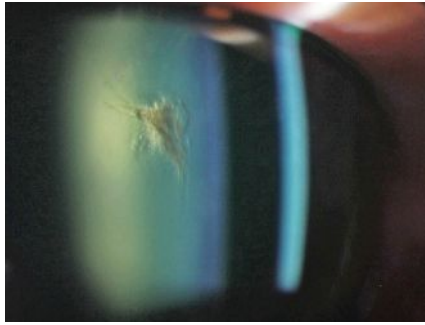
In our case, a major concern at this point was the development of an intraocular infection. Penetrating ocular trauma, intraocular surgery, intraocular injections and endogenous sources can all lead to infectious endophthalmitis.³ Post-traumatic causes alone make up about 25% to 30% of all cases of endophthalmitis.⁴ The risk of endophthalmitis in open globe injuries may be mitigated by administering a tetanus vaccine (particularly if the patient's vaccination is not up-to-date and there was non-sterile trauma), systemic oral, intravitreal, intraocular or topical fortified antibiotics.^{5,6}



A magnified view of the corneal laceration (A) with a dedicated cross-section shows the shelved nature of the laceration, likely allowing the wound to seal on its own (B).

About Dr. Bozung

Dr. Bozung works in the Ophthalmic Emergency Department of the Bascom Palmer Eye Institute (BPEI) in Miami and serves as the clinical site director of the Optometric Student Externship Program as well as the associate director of the Optometric Residence Program at BPEI. She has no financial interests to disclose.



A small focal cataract is present, indicating penetrating ocular trauma.

Another concern with our patient was the risk of lens-induced inflammation, also known as a phacogenic or phacoanaphylactic reaction. This happens when lens proteins, believed to have immune privilege, are exposed to the rest of the intraocular structures. This occurs in only a few settings, such as a hypermature cataract with leakage of lens proteins through the capsule, incomplete removal of lens material during cataract surgery or after traumatic violation of the lens capsule.⁷ Phacogenic inflammation can lead to chronic uveitis, glaucoma, hyphema, corneal edema, vitritis or cystoid macular edema if not treated promptly.⁸ Management typically involves removing all inciting lenticular material and initiating topical anti-inflammatory agents.^{9,10} Vitrectomy may be performed in some cases to rule out infectious endophthalmitis or if lens material has migrated into the vitreous chamber.¹¹

Our patient was given oral levofloxacin in the emergency room on the day of her presentation, and fortified topical antibiotics, vancomycin and tobramycin were prescribed. She was also advised to start topical corticosteroids and mydriatic drops to minimize inflammation. Intravitreal antibiotics were not initiated at this point given the general lack of inflammation inside the eye. The patient was monitored closely over the following weeks and fortunately did not appear to have any increase in

inflammation, pain or intraocular pressure. Cataract surgery was scheduled for one month later.

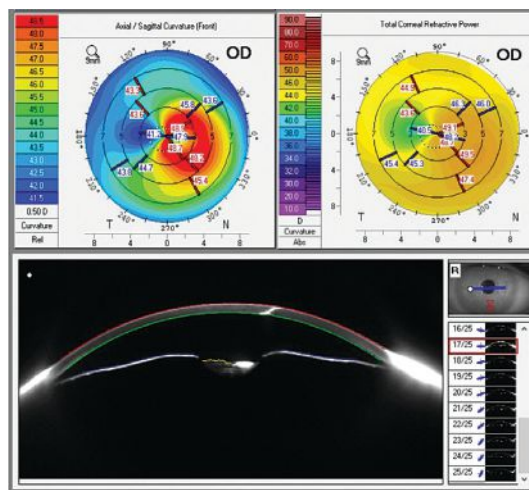
Since globe trauma increases the risk of any intraocular procedure, including cataract surgery, there are some important points to consider when planning for surgery and educating the patient on potential complications and outcomes. “Capsular integrity is of utmost importance when evaluating a patient with corneal perforation. We can assume capsular integrity is violated when cortical or lenticular material is found in the anterior chamber. Another clue is assessing for phacodonesis, as this may indicate direct trauma to the lens. An important point, however, is that it may be difficult to visualize these signs given the robust inflammation and corneal haze one may see on presentation,” says Zubair Ansari, MD, the surgeon in this patient’s case. “As a general rule of thumb, expect the unexpected when it comes to traumatic cataract. Traumatic cataracts tend to have higher rates of phacodonesis, vitreous prolapse and posterior capsular rupture.”

As far as educating the patient on postsurgical outcomes, Dr. Ansari notes that a thorough preoperative conversation about expectations is important given the higher risk of complications.

These patients may often require a secondary or sulcus-placed intraocular lens, which can make refractive outcomes less predictable. Additionally, this particular patient had paracentral irregular corneal astigmatism that would likely lead to decreased visual quality even after the cataract was removed. Since the astigmatism was non-central and irregular, a toric or multifocal lens was not appropriate. The patient underwent a carefully performed cataract surgery, in which the anterior capsular violation was incorporated into the capsulorhexis, and a standard monofocal lens was placed in the capsule. She was advised to consider a rigid gas permeable contact lens after surgery for the best visual outcome.

Takeaways

This case highlights the importance of a careful examination of all parts of the eye in ocular trauma. Penetrating ocular traumas can present with severe or minimal-appearing injuries, but they all carry an elevated risk of infection and potential complications. Our job as primary eyecare doctors is to fully document the eye’s initial status, limit and carefully watch for complications and educate patients on potential risks and outcomes. With prompt and thorough care, many patients can still obtain favorable visual outcomes. ■



Corneal topography and anterior segment Scheimpflug imaging reveal the irregular corneal astigmatism affecting the visual axis (top) and the full-thickness corneal laceration, seen as a hyper-reflective cut through the cornea (bottom).

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BY PAUL M. KARPECKI, OD
CHIEF CLINICAL EDITOR

OCULAR SURFACE REVIEW

Making the Grade

Studies show promising results for CyclASol, a new medication to treat DED that could be approved next year.

Although the market may be saturated with dry eye disease (DED) treatments, there is a new medication with the potential to separate itself from the rest. Last month the FDA accepted a New Drug Application (NDA) for CyclASol, a proposed treatment for DED, with a potential FDA approval of June 2023. This means, based on an initial review, the FDA considers the NDA complete for full review.

While calcineurin inhibitor immunosuppressants have been with us for more than 18 years, I believe this one is unique enough to make a difference and stand out for our patients.

CyclASol

This medication has unique components and clinical findings that are worth noting. While cyclosporine A is a known potent anti-inflammatory and selective immunomodulatory, it is extremely lipophilic, or non-water-soluble. Some companies have been successful using nanocellular spheres (Cequa, Sun Pharmaceuticals) to engulf the cyclosporine molecule and deliver it to the proper tissue's sites, but others, like generic cyclosporine in Canada, have failed due to this highly lipophilic issue. In the case of CyclASol, it is completely soluble in a solution known as perfluorobutylpentane, a novel, water-free carrier, which allows for bioavailability at the target tissue and improves efficacy. This novel carrier of CyclASol contains no

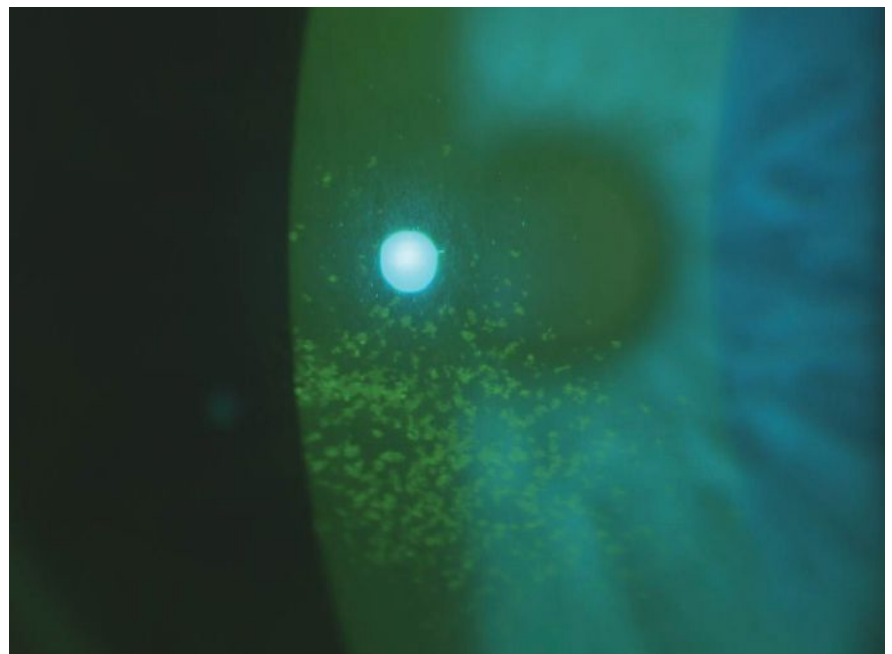
oils or surfactants and is preservative-free. Research shows that it improves tolerability and decreases visual disturbances.¹

Presentation

The NDA is supported by safety and efficacy results in over 1,000 DED patients from four clinical studies: a Phase II dose-finding study, the ESSENCE-1 and ESSENCE-2 trials and an open label extension study lasting over one year. The patient population investigated had significant ocular surface damage or staining, low Schirmer's test scores and high symptom scores, characterizing

them as moderate to severe, predominantly aqueous-deficient, DED patients.

In ESSENCE-1 and ESSENCE-2, CyclASol demonstrated a clinically meaningful and statistically significant improvement in numerous DED findings.¹ It showed a statistically significant reduction in total corneal fluorescein staining scores over vehicle as early as day 15, which was the first post dosing study visit. Differences in total corneal fluorescein staining were also significantly superior over vehicle at the primary endpoint visit on day 29. The central region of the cornea benefitted most from CyclASol treatment. Conjunctival staining scores also improved statistically over vehicle at day 29. The previous Phase II study showed that the effects on the ocular surface are greater and onset was faster compared with Restasis, which was used as comparator.²



Patients with central corneal staining, as seen here, benefitted most from CyclASol treatment in the drug's clinical trials.

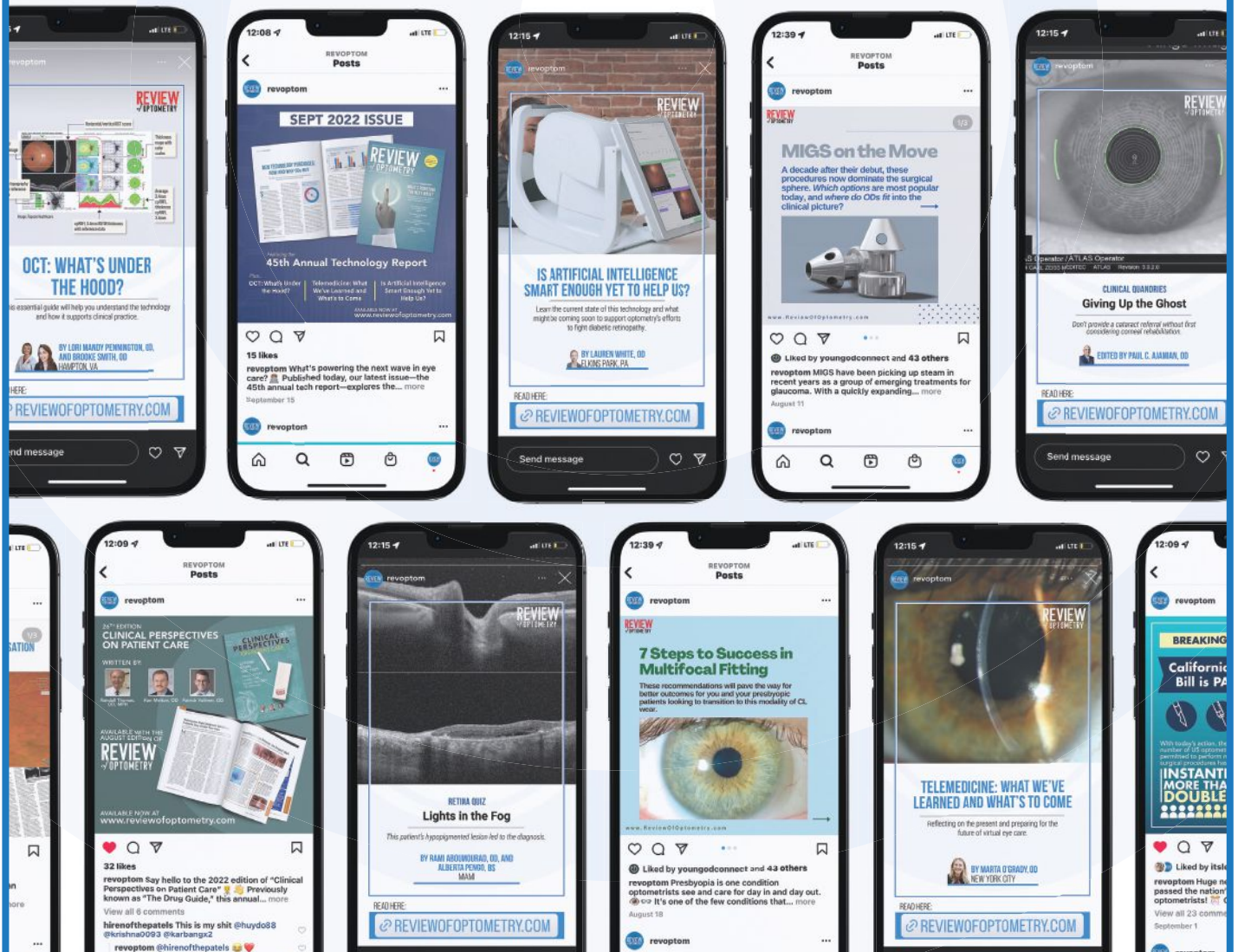
About
Dr. Karpecki

Dr. Karpecki is medical director for Keplr Vision and the Dry Eye Institutes of Kentucky and Indiana. He is the Chief Clinical Editor for *Review of Optometry* and chair of the New Technologies & Treatments conferences. A fixture in optometric clinical education, he consults for a wide array of ophthalmic clients, including ones discussed in this article. Dr. Karpecki's full disclosure list can be found in the online version of this article at www.reviewofoptometry.com.

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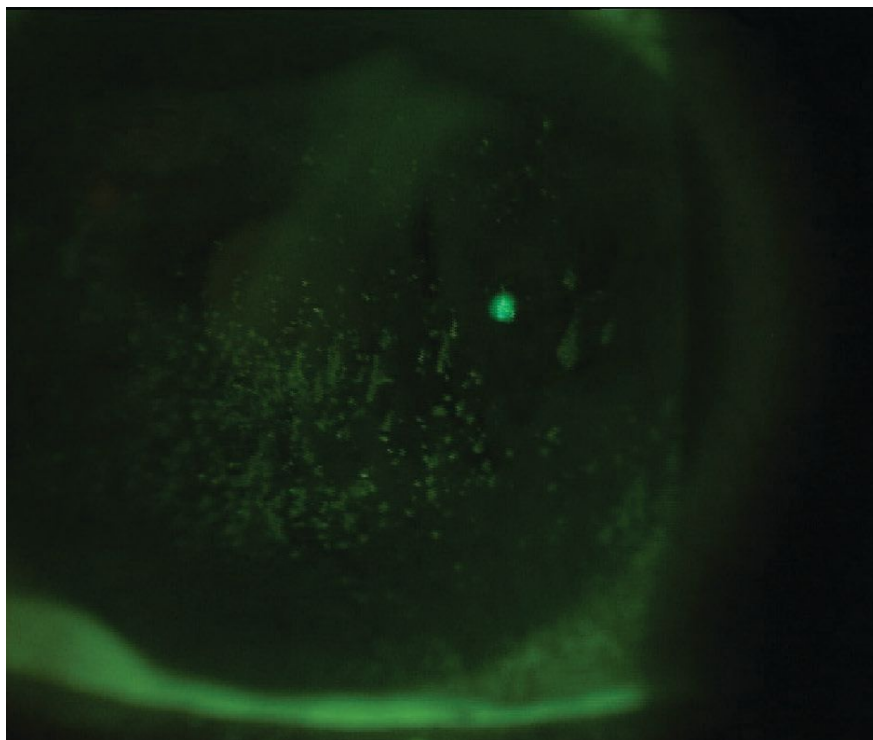


A novel aspect of this study is that it included responder analyses for total corneal fluorescein staining to evaluate whether the results were clinically meaningful for the patient. A responder was defined as an improvement of three or more grades on the NEI scale. Such a difference is considered immediately noticeable and clinically relevant, according to experts in the field. A total of 71.6% of the patients responded within four weeks with an improvement of three or more grades in total corneal staining. The proportion of responders was statistically significantly higher compared with vehicle-treated patients in both studies. Notably, responders also showed improvements in almost all symptoms compared with non-responders at day 29, underlining the clinical importance and correlations to symptom improvement at this level of cornea staining reduction.²

Ocular surface damage identified via corneal staining is an important DED indicator and requires treatment. Corneal staining has been recognized by some cornea specialists as the single most important clinical sign of DED, as it indicates the level of epithelial damage and visual impairment.³

“Patient acceptance and comfort is often a challenge using DED therapies, including generic forms of cyclosporine. This may be one of the larger differentiators of CyclASol.”

The impact of corneal staining on visual function was confirmed in the CyclASol clinical trial program. In both studies, subjects with high central corneal staining at baseline benefited from CyclASol with a statistically significant improvement in their blurred vision score. CyclASol also showed positive effects on tear production. In both studies, statisti-



Nearly 72% of CyclASol patients presenting like this could expect three or more grades of improvement on the NEI scale.

cally significant more patients using CyclASol showed an increase of ≥ 10 mm from baseline in Schirmer’s tear test score (Schirmer responder analysis), confirming a known effect of cyclosporine on the ocular surface.

Over the 52-week treatment period, all measurable effects of CyclASol were maintained and even improved for the majority of endpoints. Notably, all symptom scores reached their minimum at the last visit after one year of treatment with CyclASol, indicating continuous symptom improvement and the patient benefit of a chronic treatment.

Patient acceptance and comfort is often a challenge using DED therapies, including generic forms of cyclosporine. This may be one of the larger differentiators of CyclASol. High tolerability of CyclASol was demonstrated in both studies using drop comfort patient ratings, which show comfort level similar to that of aqueous-based artificial tears. Additionally, more than 80% of all patients selected positive descriptors when describing how the medication feels on the eye, with

the most frequent descriptors being “comfortable, smooth and soothing.” The most common adverse reaction or side effect observed was instillation site discomfort. All but one patient rated it as mild.

Patients looking for relief are likely to cheer the release of CyclASol, if the drug gets the green light from FDA. Based on this clinical data, CyclASol seems to be effective in treating both signs and symptoms of DED with an excellent tolerability profile. The rapid onset of effect, the magnitude of improvements on corneal epithelial damage, the comfort or symptom scores and relatively low adverse event profile are exciting potential differentiators to existing therapies. ■

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Made from Scratch

A patient's pet was the culprit of her condition.

BY RAMI ABOUMOURAD, OD, AND JOSHUA BLACK, OD

MIAMI

A 27-year-old Caucasian female presented to our emergency department with acute painless loss of vision in her left eye for 12 days. Five days prior to vision loss, she developed a fever, migraine, chills and myalgia. She initially presented to a local provider who referred her to a nearby emergency department, where she underwent extensive neuroimaging and serology testing.

Her past medical, ocular, social and family history were unremarkable. She was not taking any medications and had no known environmental or drug allergies. An extensive review of systems revealed recent weight loss attributable to her illness and exposure to her one kitten at home with no known bites or scratches.

Her visual acuity was 20/25 OD and 20/100 OS. Extraocular motilities and confrontation visual fields were full OU. Her pupils were equally round and reactive with no relative afferent pupillary defect, and her Ishihara color plates were full in OU. Intraocular pressures were 15mm Hg OD and 13mm Hg OS.

The patient's anterior segment examination was unremarkable, notably with no anterior chamber cell or flare OU. Posterior segment contained rare vitreous cell OD and 1+ vitreous cell OS.

Fundus imaging and OCT are also available for review (Figures 1-4).

Take the Retina Quiz

1. Which of the following is true of the posterior segment imaging?

a. There is an exudative macular neovascular lesion in the left eye.

b. There is multifocal chorioretinitis in both eyes.
c. There is optic nerve edema in the right eye.
d. There is retinal vasculitis in both eyes.

2. What is the most likely diagnosis?

a. Cat scratch disease (CSD).
b. Diffuse unilateral subacute neuroretinitis.
c. Lyme disease.
d. Syphilis infection.

3. What organism is the cause of the suspected diagnosis?

a. Bartonella henselae.
b. Borrelia burgdorferi.
c. A nematode.
d. Treponema pallidum.

4. Which of the following is NOT a possible ophthalmic manifestation of the suspected organism?

a. Conjunctivitis.
b. Chorioretinitis.
c. Neuroretinitis.
d. All of the above are possible ophthalmic manifestations.



Fig. 1. Optos widefield fundus photography of the right eye.

Fig. 2. Optos widefield fundus photography of the left eye.

About Dr. Dunbar

Dr. Dunbar is the director of optometric services and optometry residency supervisor at the Bascom Palmer Eye Institute at the University of Miami. He is a founding member of the Optometric Glaucoma Society and the Optometric Retina Society. Dr. Dunbar is a consultant for Carl Zeiss Meditec, Allergan, Regeneron and Genentech.



“ I didn't realize
STARS
were little dots that twinkled ”

—Misty L, *RPE65* gene therapy recipient

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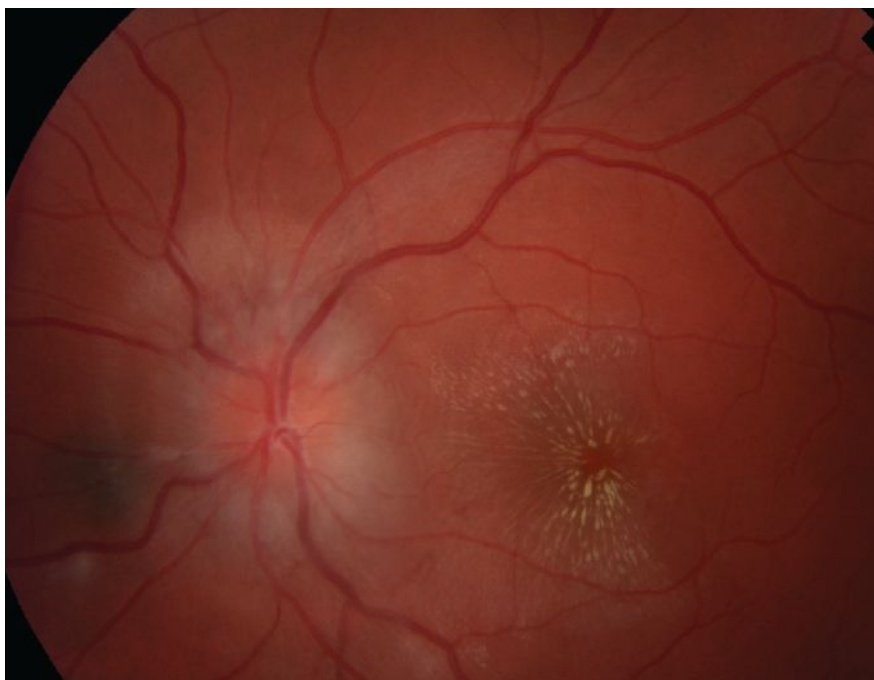


Fig. 3. Topcon fundus photo of the posterior pole of the left eye.

5. Which of the following is true?

- a. The macular star is composed of a sub-RPE drusenoid material.
- b. Gass first proposed that the macular serous detachment seen in neuroretinitis occurs secondary to leakage from the optic disc and should not be classified as a retinal vasculopathy.
- c. Neuroretinitis should be treated empirically with oral valacyclovir if a viral-like prodrome precedes the presentation.
- d. Surgical consult to oculoplastics should be considered on initial presentation for optic nerve sheath fenestration.

For answers, see page 98.

Diagnosis

Fundus exam revealed multifocal chorioretinitis OU (OS>OD) and optic nerve edema with macular star formation OS. The patient received an MRI scan of the brain and orbits with and without contrast as well as MRA and MRV of the brain without contrast at an outside hospital, all of which were normal.

Serology testing was significant only for *Bartonella henselae* IgG titer of 1:640 and IgM titer of 1:200. The patient was thought to have developed a bilateral posterior uveitis and unilateral neuroretinitis secondary to *B. henselae* infection.

Discussion

B. henselae is a gram-negative intracellular bacilli found worldwide responsible for cat scratch disease.¹ Cats are the primary reservoir for *B. henselae*, and cat fleas are the main vector for transmission.¹ Human infection occurs through scratches or bites that pierce the skin, or cat saliva on open skin lesions.¹ Although they usually show no symptoms, 40% of cats carry *B. henselae* at some point in their lives with kittens younger than one year being more likely to have the infection and spread it to humans.²

Primary inoculation results in a local papule that develops within several days at the scratch site and is associated with regional lymphadenitis.³ Within a few weeks, disseminated infection may occur resulting in a “viral-like” prodrome consisting of fever, myalgia, chills, headache, malaise and weight loss.³ *Bartonella* infection is more common in children and young adults; immunocompromised patients may develop life-threatening complications such as endocarditis and encephalopathy.³

Ocular involvement is seen in 5% to 10% of patients with CSD, and *Bartonella* remains the leading cause of neuroretinitis.^{4,5} In 5% of infections, the eye is the primary inoculation site and the individual may develop Parinaud’s oculoglandular syndrome, which is classically characterized as a unilateral follicular conjunctivitis with ipsilateral tender pre-auricular lymphadenopathy.⁴

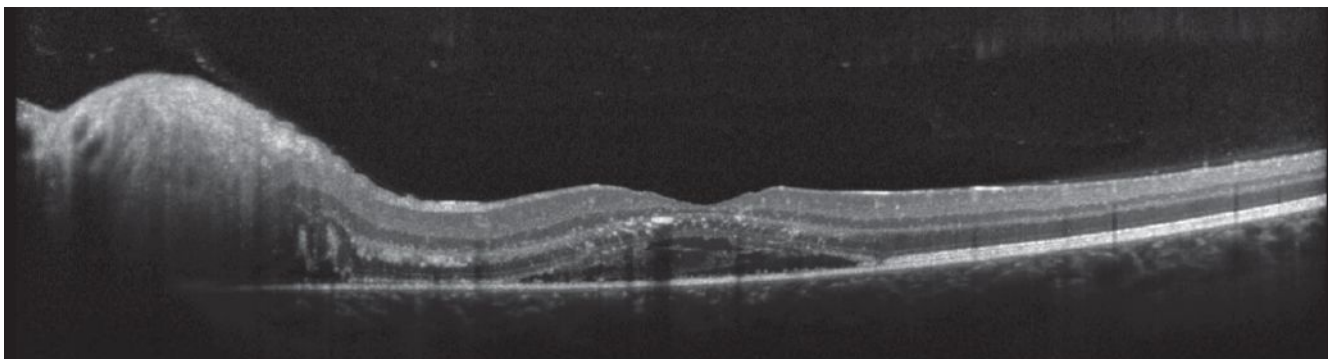


Fig. 4. Heidelberg OCT of the left macula.

Posterior ophthalmic manifestations of *Bartonella* include hypopigmented chorioretinal lesions (83%), optic disc edema (46%) and optic disc edema with macular star formation (43%).⁶

Interestingly, the white chorioretinal lesions are the most commonly seen posterior segment manifestation of *Bartonella* infection and are thought to represent choroiditis, inner retinitis or chorioretinitis that can be present even in the absence of neuroretinitis.⁶ These lesions fade slowly and result in chorioretinal atrophy.¹

Neuroretinitis is an optic neuropathy characterized classically as a triad consisting of vision loss, optic disc edema and serous retinal detachment with the subsequent appearance of an exudative macular star. It was first described by Leber in 1916, who believed the etiology was retinal in nature; however, Gass later demonstrated that the maculopathy is actually secondary to vascular leakage in the optic nerve with the

use of fluorescein angiography.⁷ The term “neuroretinitis” later became preferred for describing infectious causes of this presentation.⁷

B. henselae IgG titers exceeding 1:256 are confirmatory.¹ While mild CSD is typically self-limiting in an immunocompetent individual, neuroretinitis is a manifestation where treatment is indicated.¹

There is controversy regarding the preferred antimicrobial agent as well as the use of systemic corticosteroids. Immunocompetent adults are typically prescribed doxycycline 100mg by mouth twice a day for two to four weeks.¹ Longer treatment may be required in immunocompromised patients, and children may be prescribed azithromycin.¹ A recent review suggests that patients with severe vision loss may have some benefit from four to six weeks of doxycycline combined with rifampin 300mg by mouth twice daily.⁸

The patient was made aware of the diagnosis and started on doxycycline

100mg twice daily for four weeks with close follow-up. ■

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ABOUT THE AUTHORS



Drs. Aboumourad and Black currently practice at Bascom Palmer Eye Institute in Miami. They have no financial disclosures.

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► ASSISTIVE TECHNOLOGY

Digital Device for Amblyopia Aids Vision

Eye patching—the longstanding, arguably outdated gold standard of amblyopia treatment—is associated with a handful of adverse effects in children, including skin irritation, low self-esteem and noncompliance.

In response to the desire for alternative treatments, several companies have developed digital therapeutic devices in recent years that use various types of software to help train patients' eyes and improve their vision. One company entering this market, NovaSight, recently announced the FDA clearance of its new eye-tracking-based amblyopia treatment device, called CureSight. Designed for at-home use, developers say the device helps amblyopic eyes learn to work simultaneously while a video of the child's choice is streamed through the red-blue treatment glasses.

The treatment works by blurring the center of vision of the image shown to the strong eye, encouraging the brain to complete the image's fine details and consequently training both eyes to work as a team, according to a company press release. Children are required to complete four months of treatment, with a minimum of 18 hours per month. The device's cloud connection allows for remote monitoring of treatment reports by the patient's eyecare provider via a web portal, NovaSight notes.

In one of the company-led clinical trials, of the patients who followed up through 16 weeks, 79% in the CureSight group had a BCVA improvement of two lines or more in their amblyopic eye compared with 61% of patients who wore an eye patch.

The company also says that the treatment can be billed through three CPT codes, perhaps making it accessible to a broader range of patients.

New Upgrade to Eyedaptic Low Vision Smart Glasses



Following the release of Eye4 smart glasses last fall, the company Eyedaptic recently introduced its latest version of the low



vision aid, duly named Eye5. Similar to the previous model, the augmented reality glasses are tethered to a handheld cell phone—provided by the company—allowing users to take advantage of two cameras—one in the smartphone and one in the glasses—to help patients with central vision loss from retinal conditions such as AMD and diabetic retinopathy better see and navigate their environment.

The new facial detection capability using artificial intelligence software is the main feature that sets Eye5 glasses apart from previous models, the company explained in a press release. As with the previous model, Eye5 features an all-in-one custom user interface, auto zoom mode, image stabilization and contrast enhancement. The embedded camera in the new device also functions the same: it automatically enhances visual images by capturing the wearer's environment and manipulating the pixels, redisplaying the image in higher resolution.

Eye5 smart glasses are designed with the same lightweight material as Eye4, weighing in at only three ounces to enhance user comfort and discreetness of wear, the company says.

► DIAGNOSTIC DEVICES

Course Helps Techs Master OCT Skills

If you have a Topcon Maestro OCT and want your practice to get more out of it, your techs can now take a class to learn the ins and outs even better. The company recently announced that they have begun offering a free course—the Maestro2 OCT

Certification Course—designed to teach technicians how to capture better scans and interpret the findings on the Maestro2 robotic OCT and color fundus camera. The course also grants two continuing education credits upon completion.

The company notes that up to three technicians per clinic can participate in the course, which can be completed remotely using a computer. A variety of topics are covered, such as tips for capturing higher-quality scans, basic retinal and optic nerve anatomy and common retinal and optic nerve diseases, according to Topcon's press release. The company says that the course is available at no cost to all Maestro2 owners. ■



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Hiding in Plain Sight

When a patient has no visual problems but you notice an anomaly, what should you do?

A 54-year-old woman presented to the office with a chief complaint of needing new reading glasses. She had no other

ocular issues. She did not report any pain. The patient also denied trauma, systemic disease or allergies of any kind.

Clinical Findings

Her best-corrected entering visual acuities were 20/20 OD and OS at distance and 20/30 at near through her progressive bifocal spectacles. Her external examination was unremarkable, with no evidence of afferent pupillary defect. Goldmann appplanation tonometry measured 17mm Hg OU.

Refraction uncovered a stable distance refraction and the need for more add power in the bifocal (the add was properly positioned in the frame beginning at the bottom of the pupil).

While examining the anterior segment during biomicroscopy, an unexpected pertinent finding was discovered and is demonstrated in the photograph.

For More Information

Additional studies might include corneal topography to ensure the corneal surface is regular. Corneal staining with sodium fluorescein dye would permit understanding of the cornea's overall health status and level of hydration.

Your Diagnosis

What would be your diagnosis in this case? What is the patient's likely prognosis? To find out, please read the online version of this article at

www.reviewofoptometry.com. ■

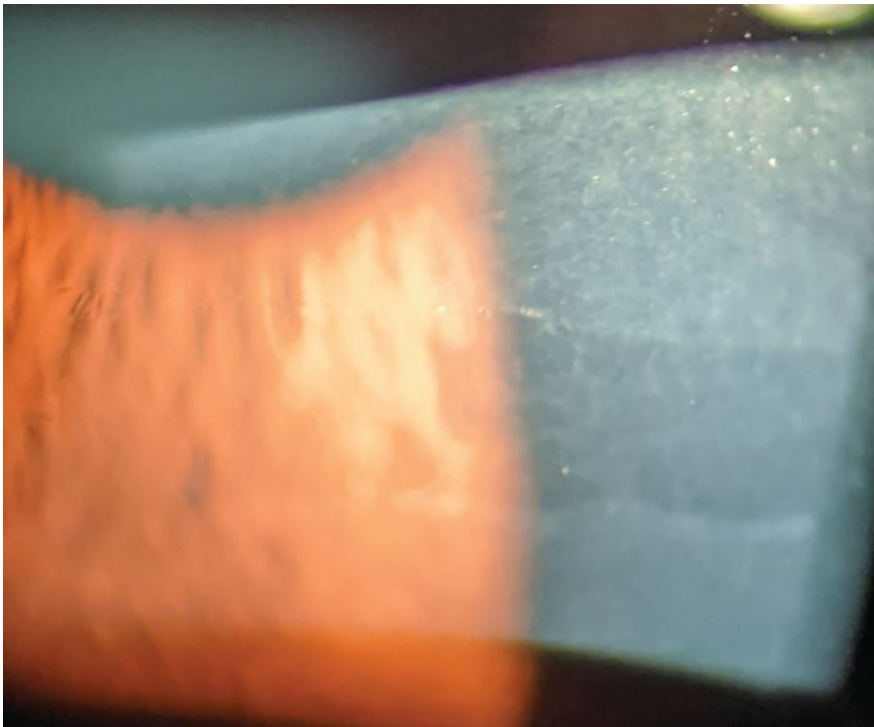


Photo: Marcus Noyes, OD

Her presentation was similar to this one from a patient with the same condition.

About Dr. Gurwood

Dr. Gurwood is a professor of clinical sciences at The Eye Institute of the Pennsylvania College of Optometry at Salus University. He is a co-chief of Primary Care Suite 3. He is attending medical staff in the department of ophthalmology at Albert Einstein Medical Center, Philadelphia. He has no financial interests to disclose.

Retina Quiz Answers (from page 92)—Q1: b, Q2: a, Q3: a, Q4: d, Q5: b

NEXT MONTH IN THE MAG

In December, we present an issue devoted to optometric surgical procedures. Articles will include:

- How to Gear Up for Advanced Procedures
- YAG Capsulotomy Tips and Tricks for ODs

- Laser Procedures for Glaucoma: When, Why and How
- Using Scalpels and Needles to Eliminate Eyelid Lesions

Also in this issue:

- Annual Income Survey: Are We Back on Track?



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