EARN 2 CE CREDITS: Positive Visual Phenomena—Etiologies Beyond the Eye, ***PAGE 58***

REVIEW® OF OPTOMETRY

January 15, 2018 www.reviewofoptometry.com

ANNUAL CORNEA REPORT

How to Heal Persistent Epithelial Defects
PAGE 38

Corneal Transplants: The OD's Role
PAGE 44

Diagnosing Corneal Infiltrative Disease
PAGE 50

CXL:

Your Top 12 Questions —Answered!

PAGE 30

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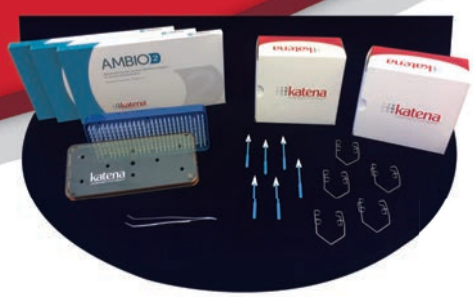
[1] Koob TJ, Lim JJ, Zabek N, Massee M. 2014. Cytokines in single layer amnion allografts compared to multilayer amnion/chorion allografts for wound healing. J Biomed Mater Res Part B 2014:00B:000-000



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VOL. 155 NO. 1 ■ JANUARY 15, 2018

IN THE NEWS

The **FDA recently approved Luxturna** (voretigene neparvovec-rzyl, Spark Therapeutics), a directly administered **gene therapy that targets biallelic RPE65 mutation-associated retinal dystrophy**. The therapy is designed to deliver a normal copy of the gene to retinal cells to restore vision loss. While the approval provides hope for patients, the $425,000 per eye price tag stands as a significant hurdle.

Scutti S. Gene therapy for rare retinal disorder to cost $425,000 per eye. CNN. www.cnn.com/2018/01/03/health/luxturna-price-blindness-drug-bn/index.html. Accessed January 4, 2018.

A study 167 patients with **suspected bacterial endophthalmitis** after cataract surgery found **intravitreal dexamethasone provided no improved visual acuity**. Patients were treated twice with intravitreal injections of 0.2mg vancomycin and 0.05mg gentamicin, followed by either 400µg dexamethasone sodium diphosphate or placebo. The four-week, 10-week, six-month and 12-month follow ups showed no significant difference in best-corrected visual acuity.

Manning S, Ugahary LC, Lindstedt EW, et al. A prospective multicentre randomized placebo-controlled superiority trial in patients with suspected bacterial endophthalmitis after cataract surgery on the adjuvant use of intravitreal dexamethasone to intravitreal antibiotics. Acta Ophthalmol. December 7, 2017. [Epub].

New research suggests a **desktop humidifier may help patients with dry eye symptoms during continuous computer use**. Investigators measured noninvasive tear break-up time (NTBUT) in patients who did and did not use a desktop humidifier for an hour of computer use and found improved NTBUT in the humidifier users compared with those without a humidifier.

Wang MT, Chan E, Ea L, et al. Randomized trial of desktop humidifier for dry eye relief in computer users. Optom Vis Sci. 2017;94(11):1052-7.

Accelerated CXL Shows Promise—and Caution

This new technology is already advancing, but not without some bumps in the road.

By Rebecca Hepp, Managing Editor

Two new studies highlight the pros and cons of accelerated corneal crosslinking (A-CXL). Researchers in Switzerland studied the outcomes of conventional (C-CXL) and accelerated corneal crosslinking (A-CXL) in a pediatric population and found A-CXL was equally effective after one year.[1]

"The potential advantages include reduced exposure time, better patient compliance and possibly lower infection risk (more patient and doctor friendly)," says S. Barry Eiden, OD, president and medical director at North Suburban Vision Consultants, Ltd., and president and cofounder of the International Keratoconus Academy (IKA).

The study included 78 eyes of 58 pediatric patients with progressive keratoconus. Half of the eyes underwent C-CXL and half had A-CXL. One year post-procedure, the researchers noted no difference in outcomes between the two groups, including uncorrected visual acuity, best-corrected visual acuity and kmax values. The treatment failure rate was slightly lower for A-CXL, at 15.4% compared with 23.1% of the C-CXL group.

However, a second study took a closer look at other A-CXL outcomes such as infection rates and found 1.3% (seven of 532 eyes) resulted in infection—while traditional C-CXL has a reported incidence of 0.0017%.[2] The researchers examined possible contributory factors in those seven cases and found young age, a pre-existing immunocompromized state, poor hygiene at the operation site and in post-op environments, long-term steroid use and poor post-op education and management were all concerns. Although the study was limited to one clinical site, it highlights the importance of patient education and careful post-op follow up with this new procedure.

These studies further highlight not just the evolving nature of treatment, but "what we at the IKA call 'the changing paradigm of keratoconus management,'" Dr. Eiden says. With access to a treatment that can halt progression and possibly prevent vision loss, clinicians have a duty to diagnose patients as early as possible and identify those at high risk of progression. Improved diagnostic technologies would be welcome additions to the evolving treatment options, such as A-CXL, for patients at risk for keratoconus, Dr. Eiden concludes.

1. Baenninger PB, Bachmann LM, Wienecke L, et al. Pediatric corneal cross-linking: comparison of visual and topographic outcomes between conventional and accelerated treatment. Am J Ophthalmol. 2017 Nov;183:11-16.
2. Maharana PK, Sahay P, Pranita, Sujeeth M, et al. Microbial keratitis after accelerated corneal collagen cross-linking in keratoconus. Cornea. November 2, 2017. [Epub ahead of print].

Beware of ISNT Rule Exceptions, Study Says

Clinicians who rely on the ISNT rule when assessing the optic nerve—for signs of early glaucoma, for example—should remember it doesn't necessarily apply to all patients. While the rule states optic nerves typically show a larger rim width inferior, superior, nasal and then temporal, a new study highlights just how often patients deviate from this: within this particular study population, only 37.0% of rim assessments and 43.8% of retinal nerve fiber layer (RNFL) measurements follow the rule, according to the researchers.

"As we know, there is a wide variance of normal nerve anatomy, which makes diagnosing early glaucoma difficult in some patients," says Jarett Mazzarella, OD, who practices in the VA Health Care System in Salisbury, NC. "Although a number of patients in the study did not conform to the standard rule, in my opinion it does not invalidate the ISNT rule since the areas of the rim we are concerned with in early glaucoma are the inferior or superior rim."

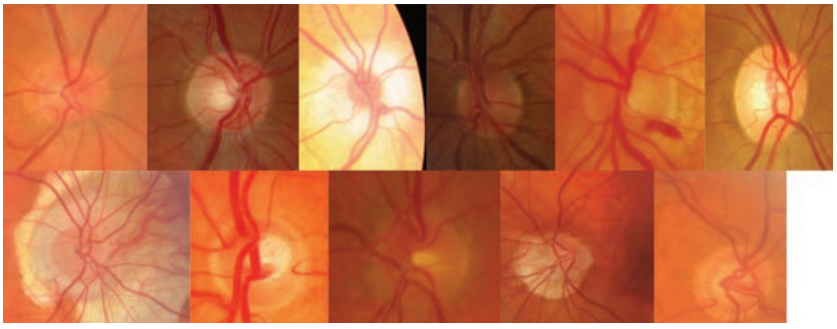
Researchers looked at 110 normal subjects and found a larger or smaller nasal sector was one of the most significant causes of deviation, with 10.9% of subjects having a wider nasal rim than inferior, 29.4% with a wider nasal rim than superior, 14.7% with a narrower nasal rim than temporal and 42.9% having thinner nasal RNFLs compared with the temporal quadrant.

"We know glaucoma patients tend to lose neuroretinal rim on the superior and inferior rims, and in this study, excluding the nasal rim to modify the rule to the IST or IS made it apply to roughly 70%," says Justin Cole, OD, of the VA Health Care System in Salisbury, NC. "So the rule still applies, but I also think we have really been using it as the 'IS' rule all along."

For clinicians assessing patients for early signs of glaucoma, Dr. Mazzarella says the findings serve as a stark reminder of the importance of obtaining baseline readings, following for change over time and "not getting stuck in the mindset of always following traditional rules."

"Early disease is the confounding factor between identifying abnormal structure vs. a normal variant. For example, we see this often with our OCT technology when a patient flags as abnormal on OCT RNFL or ganglion cell compared with the normative data values," Dr. Mazzarella says. "Many of these patients never change or progress, which usually indicates a variant of normal anatomy. It comes down to establishing a baseline for that individual patient and watching for any indication of structural or functional progression over time, especially for the normal nerve that does not look so 'typical.'"

"Each clinician must use their own judgment in identifying normal from abnormal cup-to-disc ratios and appearances, while also having the wherewithal to know that anatomical differences are common," concludes Dr. Cole.



Photos: Jarett Mazzarella, OD

Optic nerves come in all shapes and sizes, making the ISNT rule tough to follow. Can you tell which are normal, anomalous but non-glaucomatous and glaucomatous?

Poon LYC, Valle DSD, Turalba AV, et al. The ISNT rule: how often does it apply to disc photographs and retinal nerve fiber layer measurements in the normal population? Am J Ophthalmol. 2017;184:19-27.

Hot Tea's Impact on Glaucoma

Tea drinkers have one more reason to brew another pot this winter. A new study found drinking hot, caffeinated tea may be associated with a lower risk of glaucoma. Data from the 2005-2006 National Health and Nutrition Examination Survey indicates hot tea-drinkers were 74% less likely to have glaucoma. The same was not true for coffee (caffeinated or decaffeinated) decaffeinated tea, iced tea or soft drinks.

While the survey had a small number of patients diagnosed with glaucoma and didn't take into account other factors such as cup size, tea type or brewing time, the researchers speculate the tea's antioxidants and anti-inflammatory and neuroprotective chemicals may play a role.

Wu CM, Wu AM, Tseng VL, et al. Frequency of a diagnosis of glaucoma in individuals who consume coffee, tea and/or soft drinks. British J Ophthalmol. December 14, 2017. [Epub ahead of print].

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Exccessive Exercise May Raise Men's AMD Risk

A new study suggests exercising five or more times a week may increase a man's risk of neovascular age-related macular degeneration (AMD). Researchers in Japan looked at 211,960 patients ages 45 to 79 at baseline and then seven to 10 years later and found men ages 45 to 64 who exercised vigorously had a 54% increased risk of neovascular AMD compared with men in the non-exercise group. They did not find the same association in women. These results come after adjusting for factors such as age, medical history and body mass index.

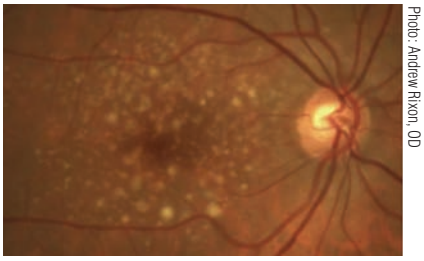

Photo: Andrew Rixon, OD

Vigorous exercise may increase a man's risk of neovascular AMD, as seen here.

While neither previous research nor this study provide further insight into the possible reasons behind the association, the investigators speculate excessive exercise may affect the patient's choroid. Still, no strong biological rationale exists for this finding yet.

"However, the authors were cautious about the results and recommended additional studies," says Sherrol Reynolds, OD, an associate professor of optometry at Nova Southeastern University College of Optometry. "Before clinical recommendations are made about limiting physical activity or discussing caution with rigorous activity and neovascular AMD, more research is necessary."

Rim TH, Kim HK, Kim JW, et al. A nationwide cohort study on the association between past physical activity and neovascular age-related macular degeneration in an East Asian population. JAMA Ophthalmol. December 14, 2017. [Epub].

Macular Damage Mechanism Discovered

Researchers at the University of Virginia School of Medicine have uncovered one of the first triggers of inflammation in macular degeneration, a common enzyme called cyclic GMP-AMP synthase (cGAS).

"This research found that, in human cell cultures and mice *in vivo*, certain proteins including the DNA sensing enzyme cGAS, played a role in activating an inflammatory immune response that ultimately leads to retinal pigmented epithelium (RPE) cell death," says Sara Weidmayer, OD, who works at the VA Ann Arbor Healthcare System in Ann Arbor, Mich., and is a clinical assistant professor at the Kellogg Eye Center, Department of Ophthalmology and Visual Sciences at the University of Michigan.

"These proteins were found in higher levels in patients with geographic atrophy (GA), so the findings suggest that they are involved in the pathogenesis of GA."

While cGAS is well known for its role in detecting foreign DNA and initiating the immune response to infections, researchers were surprised to discover its impact on dry age-related macular degeneration. Without any foreign invasion to activate cGAS, elevated levels in the RPE of eyes with GA suggests the enzyme may play a bigger part in the body's response to noninfectious human disease.

"These findings continue to provide insight into the understanding of the mechanisms of cell damage and death in patients with geographic atrophy," says Dr. Weidmayer. "Watching so many patients progressively lose their vision due to GA, with very little to offer in the way of treatment, is disheartening; the prospect of someday being able to employ a treatment to block an enzyme which drives the disease is certainly exciting for the entire eye care community."

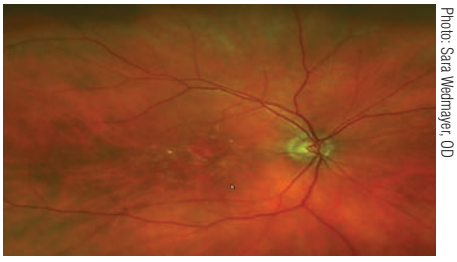

Photo: Sara Weidmayer, OD

Patient with AMD may one day have a new treatment option to combat geographic atrophy, as seen here.

"This research may prompt the development of medications to block or inhibit cGAS, which could ultimately change the trajectory of visual outcomes for GA patients," Dr. Weidmayer adds. "Hopefully this research will serve as a step on the path to the goal of individualized, precision medicine." ■

Kerur N, Fukuda S, Banerjee D, et al. cGAS drives noncanonical-inflammasome activation in age-related macular degeneration. Nature Medicine. November 27, 2017. [Epub].

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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 ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

REFERENCE

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.

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

BAUSCH + LOMB

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 µg/kg/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 mcg/kg/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 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/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 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/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 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/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 mcg/kg/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 mcg/kg/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.

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Review of Optometry January 15, 2018

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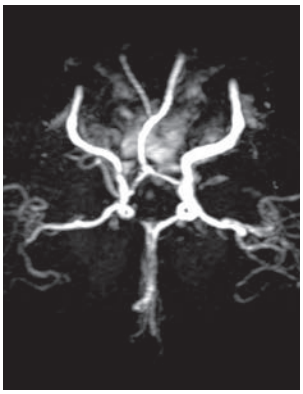

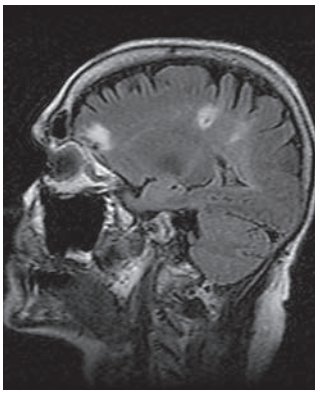

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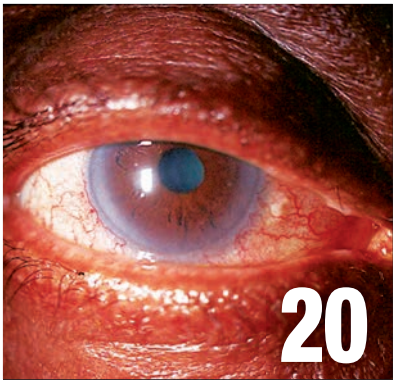

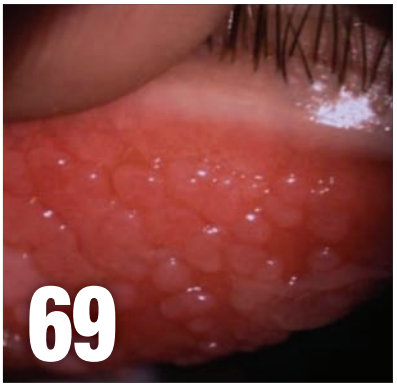

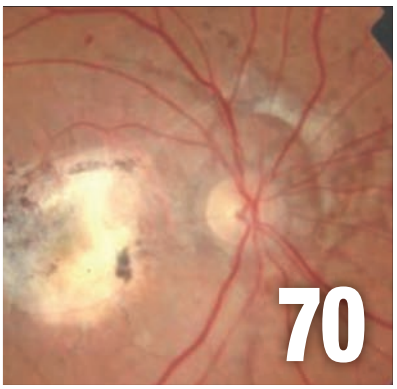

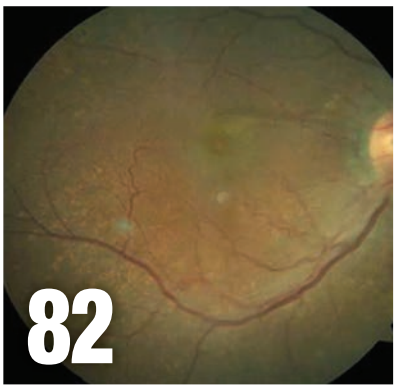

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Outlook

By Jack Persico, Editor-in-Chief

Smart Phone, Dumb App

Valuing convenience and cost savings over expertise and results enables bad habits that could prove harmful.

Warby Parker dove into the online refraction market last year with an iPhone app called Prescription Check that, as others do, looks to skim the easiest Rx refills off the top of the market. Only healthy myopes need apply. Earlier this month, the app kicked up some controversy when it was the top-featured item in Apple's app store, with the cheeky ad line, "Dr. Warby will see you now."

So I downloaded the app to size up Dr. Warby. It starts with a disclaimer that the app isn't a substitute for an eye exam. (Then why personify a bare-bones vision test with a cutesy fake-doctor persona?)

First I fielded questions about amblyopia, nystagmus, flashes and floaters, glaucoma and other complex eye health issues. By the time it asked if I have family members with "hereditary retinal problems like retinitis pigmentosa," all I could think of was Troy McClure, the beloved *Simpsons* character, a washed-up actor who would take any job, no matter how small or undignified. In a 1992 episode, Homer buys a do-it-yourself video narrated by McClure called *The Half-Assed Approach to Foundation Repair* in a foolhardy effort to save a few bucks, thinking he can tackle such a complex project himself instead of hiring a professional. Homer quickly gets flustered by Troy's complicated, jargon-heavy instructions ("Assemble the aluminum J-channel using self-furring screws") and realizes foundation repair is not a DIY project.

I'm guessing most people know as much about retinitis pigmentosa as Homer does about aluminum J-channels. If this app and others like it don't qualify as *The Half-Assed Approach to Eye Care*, I don't know what does.

After the breezy medical screening, the app got me to simulate an exam lane using my laptop. It made no stipulations about lighting conditions or the viewing angle and height of the screen—you know, minor stuff. Next it asked if I "have any complaints about the prescription" I'm currently wearing and gave me a yes/no reply and the option to leave a note for the doctor. (Nice chairside manner, Dr. Warby.) It asked for a copy of my current Rx—as if people keep that handy. I scribbled a fake one and plowed on. Finally, it walked me through a few simple acuity tests. The results will be checked by a doctor, the company says, and there's no charge if it recommends a comprehensive eye exam. But if the mysterious Dr. Warby deems that your Rx didn't change and can be refilled online, you get charged $40—and, I'm sure, are steered right into the Warby Parker frame selection app.

My Dr. Warby experience was lousy. But, hey, it was "convenient." Why should that justify it? Listen, I *wish* the public knew about RP and glaucoma and everything else so they could make better-informed decisions about their care. But apps like this encourage irresponsibility and cloak it in the guise of convenience and empowerment, which is worse than the benign neglect that keeps most people out of doctors' offices. Don't let eye health be another victim of this era's war on expertise. Tell your patients: Be *Lisa* Simpson, not Homer. Brains beat buffoonery every time. ■

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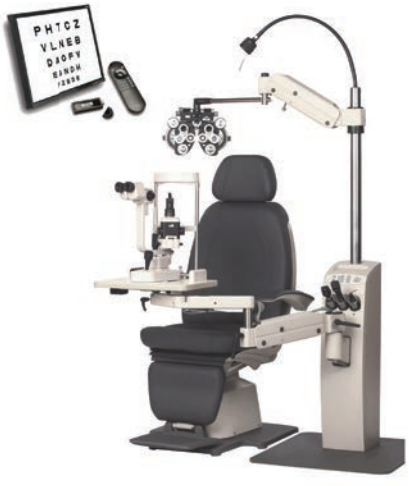

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2018: What's in View for You

A new year is an exciting time to contemplate what lies ahead. Many key technologies could greatly affect how we practice. **By Paul M. Karpecki, OD, Chief Clinical Editor**

After shelling out what seems like a month's pay for gifts, holiday parties and champagne, no one makes a New Year's resolution to "spend more money." But with so many new things coming in 2018, your resolution should be "invest in my practice." Here's a look at some promising new products.

Ocular surface issues. One of today's great opportunities is optometry's move toward the 'dental model' approach of routine preventative care. In-office procedures such as thermal meibomian gland treatments, intense-pulsed light therapy and microblepharoexfoliation will advance patient-pay dry eye care.

How to Fit it All In?

With so many new options out there, it's hard to know where to start.

First, find what interests you—whether or not it's in your comfort zone. Some of the greatest opportunities for growth occur when we're willing to embrace new things.

Second, you may need to set aside more time this year to focus your practice on these new opportunities. One way to carve out time is to outsource management aspects such as human resources, payroll and frame board management. Optometric Medical Solutions allows a doctor to outsource medical logistics like credentialing, accounts receivable, insurance verification and staff training.

Finally, stay online to protect your patients and your business. Companies like Click Optical work directly with the practice at no cost, allowing ODs to compete in online contact lens sales. Consider telemedicine where appropriate, such as EyeCare Live, which is optometry dedicated.

Outside the office, tear neurostimulation will advance, and artificial tears containing new agents such as trehalose are on the way. Hyaluronic acid–based products will gain further indications in surface healing. Punctal plugs with six months' duration may become a mainstay in the field.

In 2018 meibography may become "OCT for dry eye," and noninvasive testing (especially tear break-up time) will play a major role in care, given its accuracy, sensitivity and specificity. Point-of-care testing with the ability to know within minutes if the patient has dry eye, plus the level of inflammation and antibody biomarkers present, will change how we practice.

A just-approved product likely to take off this year is Lumify (Bausch + Lomb). This six- to eight-hour eye drop is designed to whiten eyes 300% more than traditional vasoconstrictors without the risks of rebound hyperemia or tachyphylaxis—a new option for patients who always want to be 'selfie-ready.'

Glaucoma. Not one but two new drops are on their way. The recently FDA-approved Vyzulta (Bausch + Lomb) is a prostaglandin analog that increases uveoscleral outflow plus a nitric oxide donor that works directly on the trabecular meshwork (TM) to increase outflow. Also newly approved is the first rho-kinase inhibitor for glaucoma, Rhopressa (netarsudil, Aerie), which has a multipronged mechanism of action that combines uveoscleral outflow, effects on the TM and lowering of the episcleral venous pressure.

Genetics. Spark Therapeutics just debuted one of the first ocular disease gene therapies, Luxturna, which uses an adeno-associated viral vector to transmit the proper genetic code necessary to treat rare retinal dystrophies. Avellino Labs is working on a genetic test for keratoconus that could allow for earlier treatment and stave off progression.

Retina. This year, we may see progress in treatments for other conditions once considered untreatable, such as AMD with geographic atrophy or ischemic optic neuropathy (Quark Pharmaceuticals). Further advances in OCT, ultra-widefield imaging and ultrasound technologies will keep ODs a part of the management team for retinal diseases significantly longer in the disease course before there's a need to refer out.

Vision care. Last month's approval of RxSight's light-adjustable IOL places optometry as the key doctor in determining what, if any, prescription change is required post-procedure. Presbyopia will have a new foe in 2018 if the Visability scleral insert (Refocus) gains approval. Eye alignment/prism correction will see a major boost with the NeuroLens and SightSync (eyeBrain) technologies.

There's no shortage of new technologies, treatments and business management resources to help make 2018 your best year yet. Any number of them can better position your practice and address patients' vision care needs and ocular health. ■

Note: Dr. Karpecki is a consultant for many companies mentioned here.

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Quiet Down!

This year, I'm going to shut my mouth. Or, more likely, I'll forget and use these words *more* often. **By Montgomery Vickers, OD**

Everyone knows I am the quietest person in my family. I still never shut up, so just imagine the rest of the family. Since I am the quietest person only when my siblings are around, my New Year's Resolution is to become the quietest person always and forever. Of course, I have now made 64 resolutions and only successfully kept one: to become potty trained by first grade—and that wasn't exactly a smooth ride.

The first step is quieting patient and staff interactions. I often say too much with patients, as I want them to: (a) totally understand their ocular conditions and visual status and (b) know every trivial thing I have ever done. Sometimes this makes for a very long exam; or, I just reschedule the exam and part two of my life story.

Because of my blabbering, I have learned a lot of words should be avoided when talking to patients:

1. Stupid. This should *only* be used in sentences that directly reference the patient's previous, obviously stupid, optical experience. Example: "Why did my surgeon leave me so farsighted after cataract surgery?" You know the answer.

2. Never. If you tell a patient who switches to daily disposables after wearing monthly lenses continuously for six months that they will never develop a corneal ulcer, you are doomed. Did you know most strains of *Staph.* have tiny ears? This, combined with the bacteria's black-hearted sense of humor, means the first night the patient goes to bed without their lenses for the first time in 27 years, some *Staph.* bug just hanging around at the base of an eyelash will do all he can to prove who's boss.

3. Always. If you tell two parents who are, respectively, -9.00D and -11.00D, and every family member for 70 generations has been nearsighted, that their kids will be nearsighted too, you just magically created an emmetrope. Just be quiet and let genes prevail. Another option, of course, is to prophylactically treat with myopia control techniques and take the credit.

4. Curse words. Avoid these—unless, of course, the patient is your mom, who just bought new glasses online. Then, go for it.

5. Problem. The road to practice hell is paved with docs who say to their parting patient, "Let me know if you have any problems."

6. Cataract surgery is really no big deal. The patient will kindly think, "wait until it's your eye, doc." They will also find a postoperative complication like, "My toilet flushed just fine until I had cataract surgery."

7. Names. Never walk the patient out and say, "Have a nice day, Mrs. Jones." HIPAA violation.

8. Have a nice day. They'll bend your ear telling why they won't.

9. Blonde fundus. Many patients will find that personally offensive.

10. Bifocal age. Instead, say, "your glasses should be more versatile." It will take them roughly 21 days to realize what you meant, and by then you will be on vacation.

11. Mesozeaxanthin. You will pull a muscle in your mouth. I just hurt my finger typing it.

12. Congratulations, this is the best time to be over 40! One of my in-office reading cards says that, and I am actively searching for the 27-year-old marketing guru who came up with that piece of crap.

There are so many more, but I have to start somewhere. After all, "this is the best time to be in optometry!" ■

Innovative Materials, Individualized Recommendations

By Roy A. Kline, OD
Senior Partner, Drs. Kline & Boyd, PLLC
Glenn Falls, New York

A lot of things have changed since I first opened up my practice in 1986. Back then, I opened the office with a receptionist, optician, and myself. Today we have 4 doctors and 14 highly trained staff who love working with people and deliver excellent care at every touchpoint. With a patient base of 50,000, our practice is one of the largest in the area. I credit much of our success to the very personalized care we give to our patients.

As a practitioner, I am always on the hunt for the best vision I can provide to my patients. I was a biochemist before I became an optometrist, and I am intrigued by the innovation that goes into contact lens technology. Today we have better materials, better design, and more choices than ever before for patients who wear contact lenses, including patients with astigmatism.

Despite innovations in technology, many people still believe that astigmatism and soft contact lenses do not mix. Some have been told that because they have astigmatism, they cannot wear contact lenses. Others may have tried them before but did not have a comfortable experience. For my patients with astigmatism who have tried to wear contact lenses and failed, I like to show them what a vast difference the right contact lenses can make. After I fit a patient with Bausch + Lomb ULTRA® for Astigmatism contact lenses, they sometimes look at me and smile, like, "OK, Doc, I think you're on the right track here." Those smiles can be more valuable than words.

Confidence, comfort, and clarity

Even before Bausch + Lomb ULTRA® for Astigmatism contact lenses were on the market, I already had a list of 40 patients for whom I thought the lenses would be a good fit. Of those 40 patients, 38 purchased these lenses within the first 2 weeks that we began offering them! Many patients told me, "These contact lenses are so comfortable, and my vision is incredibly sharp." My patients are impressed that they are able to maintain both comfort and clarity of vision throughout the day.

"For my patients with astigmatism who have tried to wear contact lenses and failed, I like to show them what a vast difference the right contact lenses can make."

One of my patients, a nurse in her mid-30s, recently came in wearing a different brand of frequent-replacement toric contact lenses. She said, "I'd really like to get more wear time out of my lenses. I'm just not getting what I'd like to have. I put up with them during the day, but it's kind of a struggle." Of course, we know that patients who experience this type of discomfort with their lenses often stop wearing contacts altogether, so we need to take the situation seriously.

I offered her Bausch + Lomb ULTRA® for Astigmatism contact lenses, and then I let her experience firsthand what they could do for her. She did not even wait a full week before she expressed to my staff that she could already feel a difference. Within just 2 or 3 days, she was able to keep these lenses in comfortably all day while enjoying excellent clarity.

The family is complete

Between the thin, tapered edges, the stability of OpticAlign™ design, and the moisture maintenance provided by MoistureSeal® technology, it is an easy decision to reach into my drawer for Bausch + Lomb ULTRA® for Astigmatism contact lenses. You just know the comfort, clarity, and ease of fit will be there. My patients notice the confidence I have in the product, which helps them be comfortable and confident.

With the Bausch + Lomb contact lens portfolio completed, today we can reach out to more patients, put them in innovative lenses, and give them more choices than ever before. ■

Dry Eye Gone Awry

When you try every topical therapy in the book and still can't get resolution, you may need a systemic agent—and an ally in another field. **Edited by Paul C. Ajamian, OD**

Q I have a Sjögren's disease patient with a dry eye flare up and complications. No topical treatments have helped. What's next?

A "I saw this patient for irritation and burning in both eyes about a year ago," says Brian Den Beste, OD, of LASIK Pro Eye Consultants in Orlando. The patient, a 62-year-old Caucasian female who Dr. Den Beste had seen on and off for significant dry eye and narrow angles, had a long-standing history of Sjögren's disease and chronic fatigue syndrome.

At the time of the aforementioned visit, the patient had stopped wearing her soft contact lenses based on instructions from her primary care optometrist, but was using artificial tears 10 times a day. "I suggested a mild steroid and added oral doxycycline, as she demonstrated mild facial rosacea and chronic lid margin changes characteristic of posterior blepharitis," says Dr. Den Beste. "I thought her complaints were more inflammatory in nature rather than arising from a lack of tears."

When she returned a week later with a 3mm oval abrasion above fixation in the right eye, Dr. Den Beste stopped the steroids and placed a bandage soft lens on the eye. After a two-week period of follow-up and several different bandage lenses, not much had changed. Instead, Dr. Den Beste tried a Prokera (Bio-Tissue) amniotic graft. While the abrasion shrunk significantly over the next five days, the surrounding epithelium began to show intense staining.

At this point, Dr. Den Beste went with a bland ointment and autologous drops formulated from a 50% concentration. After using the combination every two hours for a period of three weeks in both eyes, the patient felt much better, initially. "Her punctate changes were much improved and she was much more comfortable," says Dr. Den Beste.

A week later, however, the patient came back with a large abrasion on the inferior cornea of her right eye. "The surrounding anterior stroma demonstrated white blood cell migration, so I prescribed a topical fluoroquinolone," says Dr. Den Beste. Again the patient's infiltrate resolved and she went home with a bandage lens. One more week later, though, she came back with yet another large epithelial abrasion. Also, her previous inferior lesion showed stromal thinning. "After four months of steroids, bland ointment, autologous drops, amniotic membranes, moisture chamber goggles and bandage contacts, I sent her to her rheumatologist and suggested she be given a biologic response modifier or a traditional disease-modifying antirheumatic drug (DMARD)," says Dr. Den Beste.

The Fix

Per Dr. Den Beste's request, the rheumatologist gave the patient 200mg of Plaquenil (hydroxychloroquine, Sanofi-Aventis). Within two weeks, her condition changed dramatically; the abrasions resolved and her comfort returned. "Plaquenil is an older DMARD but it is still used, especially for patients with lupus," says Dr. Den Beste. "It is not clear how the drug works, but it is thought to block pro-inflammatory pathways." According to Dr. Den Beste, large sterile ulcers that occur in the periphery can lead to extreme corneal thinning and perforations, typically in patients already on medications for serious autoimmune conditions, such as Sjögren's.

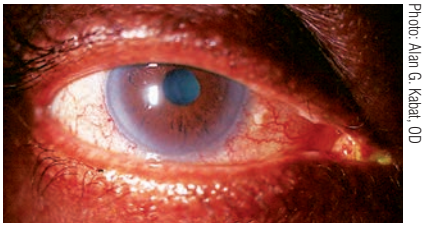

Photo: Alan G. Kabat, OD

Sjögren's patients often present with inflammatory dry eye, shown here.

"This case was unusual, however, because the patient was under the care of a rheumatologist and was thought to be doing fine systemically," says Dr. Den Beste. "It wasn't until she broke down from an ophthalmic standpoint that we recognized she needed oral medication for her rheumatologic disease."

According to Dr. Den Beste, corneal involvement in patients with severe autoimmune diseases such as rheumatoid arthritis can typically be managed with topical medications and, occasionally, oral steroids. However, sometimes they require ongoing treatment with a DMARD or a biologic response modifier such as Humira (adalimumab, AbbVie).

"As ODs, we often call on rheumatologists when dealing with severe uveitis or scleritis," says Dr. Den Beste. "The lesson here is to consider that same referral when dealing with recalcitrant dry eye and corneal inflammation." ■

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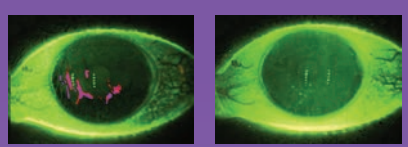

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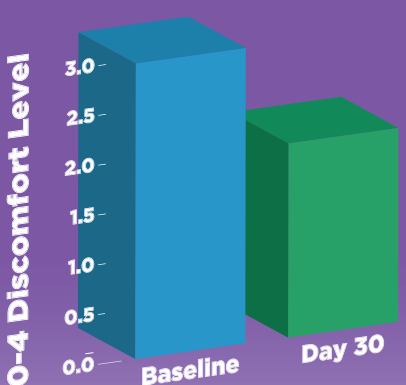

The Purpose of Prostaglandins

Two decades ago, these drugs revolutionized glaucoma therapy. Use this refresher on how they work to understand what makes the newest entrant fit in. **By Bisant A. Labib, OD**

Since their introduction in 1996, prostaglandin analogs (PGAs) have been the mainstay of glaucoma treatment due to their efficacy, once-daily dosing and limited adverse effect profile.[1] The aim of all medical and surgical glaucoma interventions is to reduce intraocular pressure (IOP), to date the only modifiable factor. Since most eye care practitioners gravitate towards the use of these drugs as first-line glaucoma treatment—and a new one has just arrived—it's important to understand exactly what a PGA is and how it works to lower IOP.

What is a Prostaglandin?

Pro-inflammatory molecules that bind to receptors throughout the entire body, including ocular structures, prostaglandins (PGs) elicit several effects. There are approximately nine types of PGs in the body, but only the PGF2 subtypes are currently targeted in glaucoma treatment because they are located directly on aqueous outflow structures and activation of this specific receptor affects aqueous humor dynamics.[2]

PGs are generally produced through the arachidonic acid pathway, in which the latter substance is released from the plasma membrane and metabolized by the cyclooxygenase enzymes. As such, they play an important role in immune system regulation and inflammation.[1] Additionally, PGs function in the constriction and relaxation of smooth muscle, adipocyte differentiation and remodeling of the extracellular matrices found throughout the body.[3-5] It is the latter—a PG's role in extracellular matrix remodeling—that yields its primary mechanism in increasing aqueous outflow to reduce IOP in glaucoma patients. PGs also elicit their known effect on smooth muscle by binding to the PG receptors located in the ciliary muscle, causing relaxation and, subsequently, increased aqueous outflow.[1,6]

Trichomegaly resulting from prolonged use of PGA for cosmesis.

Also, at the site of the ciliary muscle, the iris root and sclera, PGs induce matrix metalloproteinase (MMP) expression, a critical component in connective tissue remodeling. As a result, the extracellular matrix is modified to reduce outflow resistance and lower IOP. More recent histological studies support a similar mechanism of tissue remodeling at the level of Schlemm's canal, providing evidence that PGAs act on the conventional pathway as well, although to a lesser degree.[3,6]

PGA Tour

Topical drugs that mimic the function of naturally occurring PGs are called prostaglandin *analogs*, given their pharmacodynamic similarities to some PG-mediated processes. PGAs are stand-ins for PGs, but not identical in form or function.

Traditionally, eye doctors have relied on four topical PGAs: latanoprost, bimatoprost, travoprost and preservative-free tafluprost ophthalmic solutions.[2] While all these agents are classified as prodrugs of PGF2, only latanoprost, travoprost, and tafluprost are prostanoids. This means that following topical instillation, enzymes on the corneal surface hydrolyze the drug into a biologically active form. Bimatoprost, on the other hand, is classified as a prostamide. This difference in its chemical makeup has led to studies questioning whether this is in fact a true prodrug of prostaglandins, as the drug remains mostly unchanged following topical administration.[1]

In November 2017, a new PGA combination drug gained FDA approval. Vyzulta (latanoprostene bunod ophthalmic solution 0.24%, Valeant Pharmaceuticals) contains a PGA as well as a nitric oxide (NO) metabolite. Besides the mechanisms of PGAs described above, NO has been added to further increase aqueous outflow through the conventional pathway, by directly working on the trabecular meshwork and causing relaxation and outflow. This dual-action drug has

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been shown more efficacious than a PGA alone in clinical trials, with a mean decrease of 9mm Hg after 28 days of use in the Vyzulta group vs. a mean decrease of 7.77mm Hg with latanoprost 0.005% alone.[7] Latanoprostene bunod is nearly identical to the molecular structure of latanoprost, except that it contains a terminal NO group.[8] Because of this similarity, the side effects are the same as the current topical PGAs on the market.[9]

Side Effects of Treatment

Given the integral role PGs play in the initiation of the acute inflammatory pathway, the most common side effect of topical PGAs is conjunctival hyperemia or inflammation.[5] Clinicians should exercise caution when using topical PGAs in patients with inflammatory ocular conditions such as postoperative cystoid macular edema or uveitis.[4,10] Researchers looked at PG levels in dry eye disease and concluded that ocular injection, pain and discomfort from dryness (as well as PGA use) may be due to significantly elevated levels of PGs on the ocular surface, which correlated with patient symptoms.[11]

PGs also have an effect on adipogenesis—the differentiation of cells into adipocytes, or fat cells. Studies show that PGAs inhibit this process, and topical use decreased dermatochalasis and cause deepening of the upper lid sulcus.[4,10]

The synthesis of MMPs and the extracellular matrix remodeling effect of PGAs also occurs at the level of the cornea, with one study concluding that the use of latanoprost resulted in an increase in corneal hysteresis.[3]

Cosmetically, the use of topical PGAs results in iris hyperpigmentation and trichomegaly, or eyelash growth. The mechanism of induced iris hyperpigmentation is not well understood, but appears to be secondary to PG stimulation of iris melanocytes resulting in melanin production and melanocyte migration. These effects are often experienced following three to six months of treatment and most commonly affect hazel-colored irides.[12]

Trichomegaly occurs through PG stimulation of melanocytes in the hair follicle, as well as stimulation of follicles into the anagen, or active growth, phase.[13] The effect of these induced processes is greater lash frequency, thickness and length. This mechanism forms the basis of the FDA approval of a topical PGA for eyelash lengthening.[14]

Review of Outflow Pathways

IOP is maintained through a balance of aqueous humor production and drainage. In most glaucoma cases, it is impaired drainage that results in elevated IOP and subsequent optic nerve damage. Aqueous drainage from the anterior chamber is permissible through two mechanisms: the conventional outflow pathway and the unconventional pathway.[1]

The conventional outflow pathway, responsible for 60% to 80% of aqueous drainage, mainly involves filtration through the trabecular meshwork and Schlemm's canal, which results in the aqueous ultimately exiting through the episcleral venous system. In contrast, the remaining 20% to 40% of aqueous that is produced drains through the unconventional, or uveoscleral, pathway by diffusing through the interstitial spaces of the ciliary muscle and ultimately the suprachoroidal space.[1]

These pathways often become resistant to drainage in glaucoma patients, making them key targets for drug therapies. While PGAs have been thought to work mainly on the unconventional pathway, more recent evidence supports their role in increasing outflow through the conventional pathway as well.[1,2]

PGAs in Practice

Without PGAs, our ability to control IOP would be markedly reduced. While other glaucoma drug classes serve us well, a PGA's ability to improve aqueous outflow gives clinicians one more lever to pull in managing the delicate balance of forces that govern IOP—and, by extension, glaucoma progression.

Natural prostaglandins perform several functions; our understanding of these illuminates the mechanisms of IOP lowering as well as the side effects and contraindications we discuss with our patients. Of the nine PG subtypes, only one is currently targeted in glaucoma. Other receptors may one day serve as potential treatment sites for patients who require additional therapy. ■

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What Are You Worth?

Timely fee analysis and periodic restructuring is essential to practice success.

By John Rumpakis, OD, MBA, Clinical Coding Editor

In the world of compliance and reimbursement, we often focus on medical record compliance to survive an audit. However, how you establish a fee schedule is just as important—but rarely discussed. The schedule must be structured in an objective fashion that ensures you are paid fairly for the services you perform.

The first of the year is a great time to review your processes and make adjustments to boost your practice's success in the coming year. Let's start off by discussing how you might look at your fees in a new light.

It's Just Math, Not Rocket Science

Analyzing and setting your fees should be an analytical, objective process that is done at least twice a year. However, many physicians are unsure how to properly handle the fee restructuring process and fall back on setting fees in a haphazard fashion such as calling other doctors to price shop or, worse yet, not performing any analysis at all.

The reimbursement methodology used today has been in place since 1992 with the initial rollout of the resource-based relative value system.[1] This introduced the concept of each CPT code having a relative value unit (RVU) composed of three areas: work, practice expense (PE) and malpractice (MP).[1]

It also takes into account cost of living differences based on geographic location. It uses the geographic practice cost index (GPCI) and a conversion factor (CF) to ultimately convert a geographically-adjusted CPT RVU value into dollars. Using this system, CMS established the following formula for their physician fee schedule:

2018 non-facility pricing amount = [(work RVU x work GPCI) + (non-facility PE RVU x PE GPCI) + (MP RVU x MP GPCI)] x CF

Understandably, most people look at this complicated math equation and turn a blind eye—continuing to set their fees without understanding the implications of this system.

However, this methodology is the key to uncovering a fair amount of stealth reimbursement for your practice. Automated tools exist to help you manage this math, and some allow you to compare your fee with CMS's maximum allowable reimbursement and with the range of reimbursements from your contracted medical carriers. Armed with this information, you can then set your fee appropriately.[2]

CMS Isn't the Only Game in Town

Many make the assumption that CMS is the highest paying carrier in their area and simply set their fees as a percentage of the Medicare maximum allowable. By not including your other contracted carriers in your analysis, you may be leaving significant dollars on the table, considering their reimbursed rates may be higher than Medicare.

One Code, One Fee

Remember, the golden rule is one fee charged per CPT code. That means if I set my fee for 92004 at $150.00, I must charge everyone who gets a 92004 the same price without bias or discrimination—that includes my non-insured patients. Clinicians must respect the rules and regulations regarding time of service or prompt pay discounts; ignoring these may put you in jeopardy with your carriers. With insured patients, if the charged rate exceeds the contracted reimbursed rate from a specific carrier, the difference is generally adjusted off and not billed to the patient.

Vigilance = Profit

Just as with most things, when you pay attention to something your performance generally increases. Even small changes to your fee schedule can add up to significantly better cash flow and profitability over a year. Don't let complacency affect your bottom line. If the math seems daunting, use an automated tool to help you manage this very important, but often overlooked, area within your practice.

Paying proper attention to the value of your intellectual property can start 2018 off on the right foot, and diligent monitoring can lead to better business decisions for a long time to come. ■

Send questions and comments to rocodingconnection@gmail.com.

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Early adopters of MyDay® toric are sharing their experiences with the lens, and it is everything they had hoped for. All-day comfort. Stability. Familiar fit. Healthier modality and material. Find out more about why practitioners are reaching for them, why patients love them, and why some are saying that MyDay® toric is CooperVision's best toric contact lens yet.

WHY DO YOU REACH FOR MYDAY® TORIC? WHAT WOULD YOU TELL YOUR COLLEAGUES ABOUT THIS LENS?

McIntyre: With the shift toward fitting 1-day contact lenses, the introduction of MyDay® toric is very timely. CooperVision is known for its toric contact lenses, and they've made really good torics throughout my very lengthy career. But there is nothing better than this. MyDay® toric has the water content, the Dk, the comfort, the vision—it has everything you want in a toric, let alone a 1-day toric. I would tell my colleagues, "Just try them. You're going to love them."

Bircher: I would tell my colleagues that MyDay® toric is a game changer. Whether patients are using it to supplement their current supply, or transitioning to the 1-day modality full time, we finally have a lens that will make them very happy with the vision and comfort. And the doctor is going to be happy with the health of the eye.

"MYDAY® TORIC IS A GAME CHANGER."
DAWN BIRCHER, O.D.

Koepke: The best features of MyDay® toric are its stability and reliability. It's been very easy to fit; it settles quickly. It's stable, even as the patient is looking from left to right. Take the prescription, pick that lens, put it on, and it's likely going to work. Rarely have I had to make any adjustments for axis or power changes. And your patients are going to be happy with it. I've been really satisfied with the outcomes. It has been spot on.

Browning: MyDay® toric is CooperVision's best lens to date. It has been a great lens. We've always wanted Biofinity® toric in a daily disposable. Now we have a great lens that is going to be very clear, consistent, and extremely comfortable to wear all day long. MyDay® toric has already become my first choice and my favorite for fitting daily disposable torics. We get the benefits of the all-day comfort of Biofinity®, now with the advantages of daily disposables to have that fresh, clean lens on the eye every day.

Dawn Bircher, O.D.
Kansas City Eye Clinic
Overland Park, KS

David Browning, O.D.
Drs McIntyre, Garza, Avila and Jurica, O.D.
Corpus Christi, TX

Liza Koepke, O.D.
Rancho Santa Margarita Optometry
Rancho Santa Margarita, CA

John McIntyre, O.D.
Drs McIntyre, Garza, Avila and Jurica, O.D.
Corpus Christi, TX

"MYDAY TORIC IS COOPERVISION'S BEST LENS TO DATE."
DAVID BROWNING, O.D.

HOW SIMILAR IS THE PERFORMANCE OF MYDAY® TORIC TO BIOFINITY® TORIC?

Browning: Biofinity® has been the gold standard for all toric lenses. It's been fantastic as far as not rotating, very good vision, very good comfort. In my practice, we compare everything we have to Biofinity®. Most daily disposables rotate more, so patients will experience more vision fluctuation, and that's why they end up going back to monthly lenses—for more stable vision. But then they complain that they're not as comfortable. Now you don't have to worry. With MyDay® toric, you have the stability of Biofinity® with the advantages of a daily disposable. It has been a great lens for us.

McIntyre: We fit a lot of Biofinity® torics, so we were interested to see how MyDay® toric would perform vis-à-vis the Biofinity® toric. They have been very similar in the fitting, the speed of the adjustment, the comfort. In every way we could monitor, Biofinity® toric and MyDay® toric performed equally.

Koepke: For my patients going from Biofinity® toric, which is a great toric lens, putting them into the MyDay® toric was actually very easy. They fit very similarly. They're both very comfortable, and the stability has been great.

HOW HAVE YOUR PATIENTS RESPONDED TO MYDAY® TORIC?

Koepke: My patients tell me that MyDay® toric is a homerun when it comes to comfort. It's been really soft, it's easy for them to handle and get in and out, and they're getting great all-day wear.

Browning: The number one complaint for all contact lens wearers that I have seen is end-of-day comfort. They can put on almost any lens and be good for an hour or two, but to be able to sit in front of a computer or to do daily tasks, they're just done. By the time it's 5:00 or 6:00 p.m., patients want to remove contact lenses, and we've found that with MyDay® toric, patients have done so much better. They can put on the lens and not think about their contacts all day long.

Bircher: Seeing patients' reactions is what I've enjoyed most about MyDay® toric. I've had a patient for over a decade, who has always had long-term complaints about her vision and comfort in toric lenses. When I first received MyDay® toric, I instantly thought of her. When we dispensed the first lenses, you could tell she was very hesitant. She shrugged her shoulders and said, "We'll see." Within a week we got a phone call from her, telling us this was the game changer for her. She had all-day, end-of-day comfort with MyDay® toric, in addition to crisp, sharp vision. With MyDay® toric, I feel confident telling my patients that they will have the same comfort in 8-10 hours as they do at initial insertion.

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Your Top 12 Crosslinking Questions—Answered!

New to corneal collagen crosslinking? This Q&A guide from Wills Eye Hospital will help prepare you to manage keratoconus patients in the new era.

By Clark Chang, OD, MSA, MSc, and Christopher J. Rapuano, MD

For many eye care providers and patients, keratoconus (KCN) management can feel like maintaining an undesirable status quo. Due to advancements in specialty contact lens technologies, corneal grafts are now only necessary for 10% to 20% of KCN patients.[1] Notwithstanding, these patients still scored similarly to those with advanced macular degeneration on the National Eye Institute's visual function questionnaire in CLEK Study (Collaborative Longitudinal Evaluation of Keratoconus Study).[2-5] Another report by the same group found that self-perceived quality-of-life scores for KCN patients continue to decline over time.[6] With postulated KCN prevalence reaching one in every 375 individuals, disease stabilization and quality of life improvement or maintenance are top priorities.[7]

Since its development in 2003, corneal crosslinking (CXL) has quickly become the treatment of choice for KCN progression control.[8] Although CXL only received US Food and Drug Administration (FDA) approval in 2016 (Avedro's KXL System and two photoenhancers, Photrexa and Photrexa viscous), we have been able to offer CXL treatments to patients for many years at Wills Eye Hospital under the auspices of clinical trials. As a result, we comanage many of these patients with community clinicians.

Fig. 1. Christopher Rapuano, MD, performs standard a corneal crosslinking protocol with the FDA-approved KXL System.

As with any new treatment procedure, a learning curve exists for clinicians to refine patient education and selection process, as well as other perioperative management-related protocols. An open channel of communication allows our Corneal Service to help comanaging clinicians to gain clinical comfort with CXL in their KCN practices. Here are 12 common questions our partner doctors ask; the answers can help you decide on how to best educate your KCN patients on CXL.

1. What is CXL and how does it work?

Crosslinking is a polymerization process that rearranges monomers into a three-dimensional network of polymers to increase the soundness of a molecular structure. This process naturally occurs in our bodies as connective tissues gradually stiffen over time. Facilitated by the endogenous enzyme lysyl oxidase in launching the required oxidative reactions, additional covalent bonds (or tissue "crosslinks") are

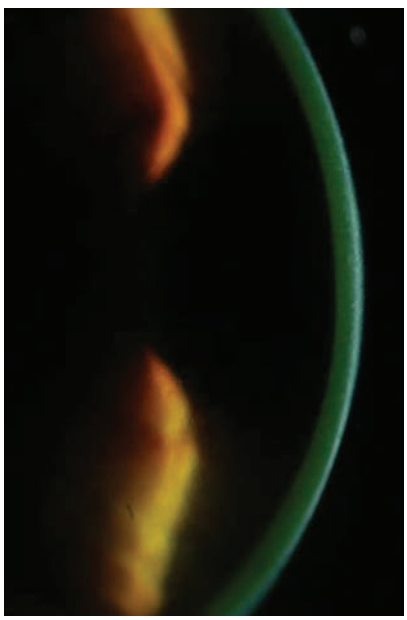
formed between and within collagen fibrils—yielding increased tissue biomechanical strength.[9]

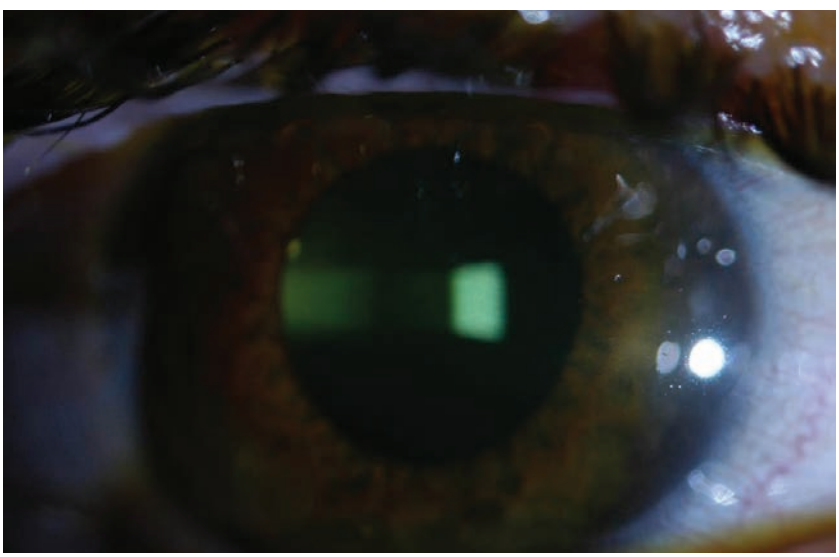
Typically, the cumulative effects of natural crosslinking reactions are slow to manifest. In the late 1990s, researchers from the University of Dresden in Germany determined that the photochemical induction process was the most clinically viable method for boosting induction of crosslinks in the cornea, bringing about CXL.[8] This study used 0.1% riboflavin (with 20% dextran in solution) as the photosensitizer to absorb a carefully calibrated ultraviolet (UV) energy dose, thus converting available tissue oxygen into singlet oxygen molecules. The resultant reactive oxygen species possesses sufficient energy to activate the lysyl oxidase enzymatic pathway, leading to formation of new covalent bonds within the corneal stroma.

The study from Dresden reported that all of the 23 progressive KCN eyes treated were stabilized, with 70% showing maximal keratometry flattening by 2.01D. Since then, many studies have achieved similar efficacy with good safety profiles in KCN patients using the same CXL protocol involving epithelial removal (*Figure 1*).[10-13]

2. What is riboflavin's role during CXL?

Since the bioavailable oxygen molecules in the cornea cannot be activated by UV light directly, a photosen-





Figs. 2a and 2b. Above, saturation of riboflavin seen in the corneal stroma after riboflavin loading. Below, after 30 minutes of riboflavin loading at two-minute intervals, clinicians must check for aqueous riboflavin staining.

sitizing substance must act as an intermediate agent. Riboflavin catalyzes CXL's photochemical reactions by transferring UV energy (specifically, UVA from 365nm to 370nm) to stromal oxygen molecules, thereby converting stable oxygen molecules into a more reactive singlet form. These reactive oxygen species then initiate intrastromal oxidative reactions.

Assuming UV energy is not the limiting resource, continuous oxygen replenishment and active riboflavin molecules are essential in maintaining the energy transfer required to perpetuate the CXL process.

Additionally, saturating the cornea with riboflavin creates a "shielding effect" in which the respective UV energy levels reaching the endothelium, lens and retina are titrated to a much lower intensity than the actual cellular damage thresholds. In fact, if a riboflavin-saturated cornea is at least 400µm in thickness, the UV irradiance transmitted to the endothelium is only 0.18mW/cm^2, whereas the actual endothelial damage threshold is approximately 0.35mW/cm^2. Thereafter, the energy level projected to reach the crystalline lens and retina is even lower compared with the respective damage thresholds of these tissue layers.[14,15]

3. What is the purpose of epithelial removal in the standard CXL protocol?

The lipophilic nature of the corneal epithelium and the small pore size of its tight junctions make this layer essentially impervious to riboflavin molecules. These epithelial barrier characteristics prevent efficient and homogenous riboflavin saturation in the targeted stromal tissue.[16]

Epithelium also contains enzymes with high antioxidant properties such as ascorbate and tryptophan residues, which can prevent UV penetrance and scavenge reactive oxygen species. Moreover, the presence of an epithelial barrier slows the rate of oxygen replenishment during CXL procedures, thus reducing the total amount of new cellular crosslinks that can be created. Consequently, when the same standard CXL protocol is carried out with an intact corneal surface, the procedure's overall efficacy will be lower than anticipated. On the other hand, due to non-homogenous riboflavin saturation and reduced riboflavin shielding effects, UV transmissions delivered to the endothelium and deeper ocular tissues may be higher than previously calculated.[16,17]

Clinicians should not assume CXL is only effective when accompanied by epithelial debridement. Although transepithelial CXL (TE-CXL) applications do not currently have FDA approval, modified treatment techniques are under investigation to enhance TE-CXL efficacy.

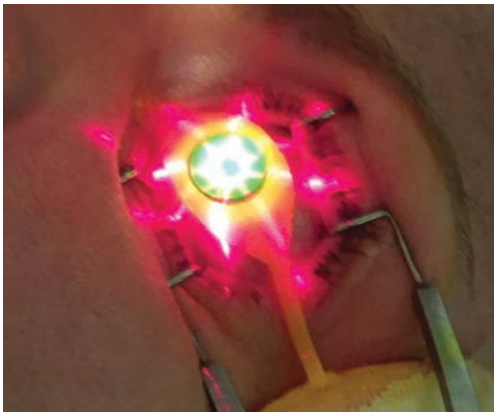


Fig. 3. Crosshair guidance is projected from KXL device onto treatment site.

4. How is the standard CXL protocol performed?

Topical anesthesia is used when removing the central 9mm of epithelium to ensure patient comfort and allow for faster, more homogenous stromal saturation of Photrexa viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) during CXL. This phase lasts for 30 minutes with riboflavin instillation in two-minute intervals.[10]

After 30 minutes, patients are examined under the slit lamp to ensure the riboflavin has saturated the intended treatment area and that it is present within the aqueous (*Figures 2a and 2b*). Per FDA approved indications, clinicians must perform pachymetry after riboflavin application to make sure the corneal thickness is at least 400µm. If it is less than 400µm, hypotonic Photrexa riboflavin should be administered every five to 10 seconds until the cornea is rehydrated to 400µm or greater.[10]

Once the appropriate pachymetry level is verified, clinicians use the KXL UV device (Avedro) for the second phase of CXL treatment, where 30 minutes of UV irradiance (3mW/cm^2) yields a total energy dose of 5.4J/cm^2.[8] During the UV emission period, Photrexa viscous is instilled in two-minute intervals while proper centration and device-eye distance are maintained by the operator. The proper KXL device position can be guided by the crosshair image projections (*Figure 3*), which aid the delivery of an optimum illumination beam profile to the treated cornea.

Excess riboflavin can be rinsed off with a balanced salt solution at the end of a treatment session. A bandage contact lens (BCL) is inserted after instillation of topical antibiotic and corticosteroid agents. The BCL should be kept on the treated eye for three to five days or until epithelial closure (*Figures 4a and 4b*).

5. What are the patient selection recommendations?

In 2016, the standard CXL protocol received labeled indications in the United States to treat patients 14 years of age or older with progressive KCN or corneal ectasia following refractive surgeries. However, when left untreated, disease severity and rate of progression are known to be more aggressive in younger patients. Therefore, the KXL system and Photrexa/Photrexa viscous can be considered for off-label use in younger patients with minimum corneal thickness of 400µm or greater. KCN patients as young as eight have been reported by clinical trials, but special informed consents must be obtained from the patients and their guardians in these cases.[18]

Although the FDA has not specified any contraindications, clinicians should exercise judgment before offering CXL to lactating mothers and patients older than 65 years of age. Also, researchers strongly recommend avoiding CXL during the course of a pregnancy. A recent study found topographic, pachymetric and biomechanical evidence of KCN progression in 100% of its pregnant patient cohort.[19] This led researchers to recommend discussing prophylactic CXL with female patients prior to family planning. Some European countries have begun to proactively offer CXL to female KCN patients who are planning for pregnancy despite lack of disease progression.[20]

6. Is KCN progression necessary to recommend CXL?

Although KCN progression is part of the on-label indication for CXL treatment, certain circumstances do not require progression before a CXL consult. Female KCN patients who are planning to become pregnant and patients at a high risk for progression are just two potential clinical examples.[19,21]

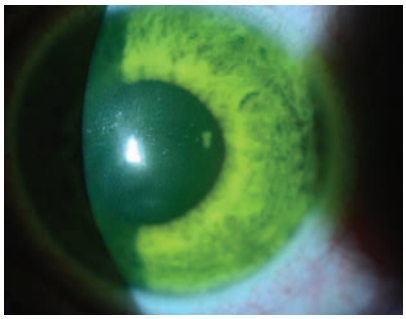


Fig. 4a. Here, a bandage soft contact lens is on the eye immediately after CXL treatment on a patient where corneal riboflavin saturation is still evident.

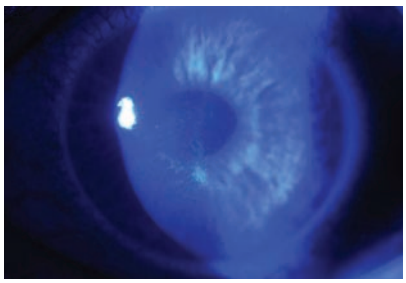


Fig. 4b. Epithelial wound closure is mostly complete on the same patient only three days after treatment with CXL.

According to the conventional KCN care model, some amount of meaningful changes in clinical parameters must manifest prior to initiating a new treatment course. However, significant progression frequently occurs before action is taken due to the lack of consensus on the exact clinical indicator and corresponding magnitude of change that constitutes disease progression. Many CXL studies define KCN progression as changes over a 12-month period in the any of the following measurements: 1D or more in maximum keratometry; 0.5D or more in myopia; 1D or more in astigmatism; or 10µm or more loss in thinnest pachymetric point.[10-12,20,22] However, with the limited accuracy of traditional topographers when imaging the irregular corneal surface and

the refractive variability of KCN patients, these guidelines may result in a higher rate of false positives.

Alternatively, one expert panel recently recommended that the presences of at least two of three criteria can establish progression: steepening in anterior corneal curvature; steepening of posterior corneal curvature; or thinning when comparing pachymetric distribution profile from periphery to thinnest point.[21] While useful, these guidelines require access to corneal tomography capable of tracking changes over time, presenting a possible challenge for some comanaging clinicians.

Given these clinical hurdles, the expert panel assembled from four supranational corneal societies concluded that CXL recommendations can be made to KCN patients with high-risk profiles, even if progression has not been documented.[21]

7. Should I consider CXL for patients older than 40?

The short answer is yes. KCN patients tend to display a slower rate of progression or even stabilization in their fourth or fifth decade of life—likely a byproduct of age-associated crosslinking. However, KCN expression is highly variable, and age alone is not always a well-defined end point for KCN. A retrospective chart review from Wills Eye Hospital found 24% of the 186 eyes newly diagnosed with KCN belonged to patients aged 40 or older.[23]

In addition, given that post-surgical ectasia can occur at a later point in life than a typical KCN patient, clinical consensus has not defined an age range for when ectasia typically occurs and when progression may slow down. Thus, clinicians should refrain from using age as an absolute contraindication for CXL candidacy.

8. What are the general CXL postoperative findings and expectations?

The initial phase of recovery from standard CXL is much like any procedure involving corneal epithelial removal. Although BCLs offer therapeutic protection and enhanced patient comfort, most patients still experience some ocular discomfort or pain until the epithelial defect closes, which usually occurs in three to five days.[24]

After epithelial closure, visual acuity generally worsens or greatly fluctuates throughout the first month before slowly returning to baseline by the third month. Patients may experience a mild improvement in vision between months three and six or months six and 12. Additionally, a stabilization trend typically emerges as the new baseline between months six and 12.[10-12]

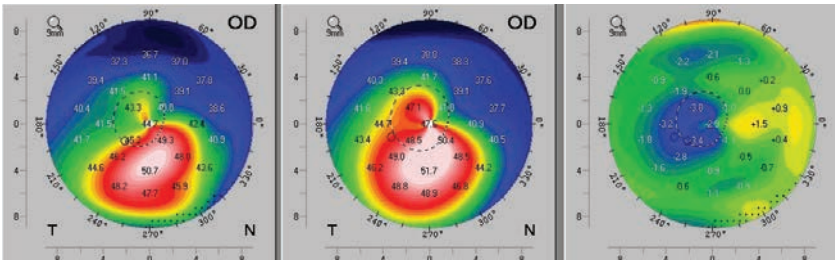


Fig. 5. An example of topographic flattening seen as early as three months after standard (epi-off) corneal crosslinking protocol. The left map shows the patient's preoperative axial topography. The center map is the postoperative topography at month three, and the right map provides a difference calculation revealing the topographic improvement at month three.

After standard CXL, keratometry, pachymetry and transient CXL haze measurements also follow a similar temporal pattern, with further steepening, thinning and reduction in corneal transparency during the first month. These trends typically reverse over the following two months, at which point patients slowly return to baseline characteristics. Sometimes these patients even experience mild improvements before reaching a plateau of stabilization (*Figure 5*).[10-12]

It's important to refrain from misconstruing these immediate postoperative trends as worsening in KCN disease or CXL failure. Overall, despite an epi-off CXL protocol, only a short period exists during the immediate postoperative recovery where patients may feel visually compromised. This is because patients are refit in contact lenses or can resume contact lens wear before they reach post-CXL stabilization.

9. Can CXL patients expect any refractive changes?

Studies have reported variable results for sphere, cylinder and spherical equivalent at 12 months post-CXL treatment. Some show statistically significant refractive changes, while others recorded no notable differences.[25-27] Researchers have reported improvements in total higher-order aberration, spherical aberration and coma as well as average topographic flattening of 1.6D.[10,28] Still, the literature provides no consistent correlations between changes in these clinical parameters and CXL treatment.

Consequently, KCN stabilization should remain the primary objective of currently available CXL protocols. Before recommending CXL, patients should be informed that contact lenses or glasses will still be required after CXL, and this management approach may improve patients' quality of life by reducing

the frustration often associated with frequent optical changes when KCN is left untreated.

10. Is CXL haze a concern?

Transient CXL haze can appear similar to post-PRK corneal haze. With experience, however, clinicians can differentiate the two entities under the slit lamp. CXL haze creates a dust-like tissue change in the anterior to mid-stromal levels, whereas PRK haze manifests in a reticulated fibrotic proliferation pattern that is localized to the subepithelial to anterior stromal layers. Given the different anatomic appearances and the self-resolving nature of CXL haze, it is unlikely to carry the same visual implications as PRK haze.[24]

Immediately after CXL treatment, confocal microscopy will reveal keratocyte apoptosis and lacunar edema in the anterior to mid-stromal area. As areas of CXL haze and stromal edema start to show improvement by the end of the first month, clinicians will see zones of optical discontinuity—or demarcation lines—with an optic section during slit lamp examination (*Figure 6*).[24]

Although glare disability is a possibility during the first six to eight weeks, transient CXL haze and demarcation line depth are often used as indicators to reflect treatment penetration and resultant stromal collagen remodeling. As keratocytes slowly repopulate, the backscattering of light starts to resolve and the areas of CXL haze begin to fade between three and six months. The haze will often become unnoticeable by one-year post-CXL. Topical steroids are often discontinued after the first few weeks following the procedure, yet most cases of CXL haze self-resolve over time without further therapeutic interventions; thus, researchers suggest

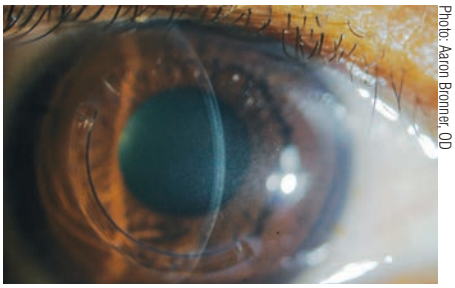


Photo: Aaron Bronner, OD

Fig. 6. The demarcation lines are visualized with optic section in a patient who received off-label treatment of CXL and Intacs corneal implant (AJL Ophthalmic).

topical steroids do not mitigate CXL haze and their long-term use is not necessary after standard CXL. However, one study proposed that topical steroids may be justified if persistent haze or stromal scarring is observed after the one-year mark.[24,29]

11. Can you perform CXL without removing the epithelium?

Standard epi-off CXL is minimally invasive and highly effective in halting KCN progression. Additionally, adverse events are uncommon after standard CXL.[10-13] However, researchers continue to investigate delivery methods to increase comfort during and after the procedure, shorten visual recovery time and reduce risks of potential infection.

Keeping the epithelium intact reduces diffusion rates of riboflavin, UV light and oxygen, all of which are essential to the photochemical reactions during CXL. Researchers have been able to bypass the epithelial barrier function by disrupting tight junctions with chemical enhancers such as benzalkonium chloride (BAK) and ethylenediaminetetraacetic acid (EDTA). These corneal enhancers are incorporated into the riboflavin solution to assist penetrance into corneal stroma. However, some studies have reported shallower demarcation lines

and reduced corneal stiffening effects after TE-CXL.[30,31]

Although several studies reported higher regression rates with TE-CXL, its rates of adverse events are also lower than those of standard epi-off CXL. Additionally, the shallower CXL treatment depth may be advantageous in eyes with thinner corneas at baseline. Patients with a low risk of progression and those who are concerned about visual recovery time may be reasonable candidates for TE-CXL.[24,30,31]

Until the efficacy of TE-CXL improves, we will continue to recommend standard epi-off CXL for KCN patients with a high likelihood of progression or aggressive clinical progression.

12. When should I refit contact lenses after CXL?

A study using confocal microscopy showed that epithelial thickness gradually returns to normal between three and six months after standard CXL.[24] However, many patients require contact lens rehabilitation to function and cannot wait six months before resuming contact lens wear.

Our personal approach is to adopt a lens fitting strategy that allows minimal to no interaction between the posterior lens surface and corneal epithelium, given the possibility of persistent haze with delayed epithelial healing or disrupted epithelial remodeling. Various lens designs can help accomplish this goal including those with corneal vaulting capacities, such as hybrid, scleral, piggyback and even custom soft lenses. From clinical experience, we have found the ideal time to consider refitting a lens is approximately four to six weeks after standard CXL or two weeks after TE-CXL. It's also prudent to stress to patients, particularly after standard CXL, that frequent refractive modifications in their contact lenses may be expected over the next six to 12 months.

The emergence of CXL has ushered in a new era of KCN management in which clinicians no longer have to assume a passive reactive management approach and offer patients only a forced choice between contact lenses and corneal grafts. With early CXL intervention for appropriate candidates and continual post-CXL monitoring, clinicians can help patients maintain their best visual function and maximally defer the possible needs for keratoplasties. Today's clinical focus should go beyond simply refitting contact lenses as KCN progresses. With early detection of KCN, access to CXL and advancements in specialty lens designs, clinicians can help their KCN patients live life to the fullest. ■

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Dr. Rapuano is chief of Cornea Service at Wills Eye Hospital. He has published several books, numerous book chapters and over 175 peer-reviewed articles, including having co-authored The Wills Eye Manual.

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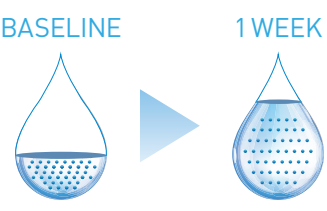

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AKORN | CONSUMER HEALTH

Fixing a Hole: How to Heal Persistent Epithelial Defects

Clinicians have a robust arsenal for treating this reccurring condition. Knowing where to start and when to switch it up is key. **By Alan Kwok, OD**

Corneal metabolism and wound healing are crucial to properly maintaining the cornea's integrity and functionality. When an insult occurs to the corneal surface, creating an epithelial defect, the complex re-epithelialization process involves limbal stem cells, cell differentiation, proliferation, migration and remodeling of the extracellular matrix.[1] Researchers believe growth factors involved in the process include epidermal, keratinocyte, hepatocyte and basic fibroblast growth factors.[2] In normal, healthy corneas, supportive therapy can help the body resolve an epithelial defect rapidly. However, healing may be delayed or halted altogether in compromised conditions, leaving the underlying stroma exposed and vulnerable to further trauma, infiltrates, infection, scarring or perforation.[3] A persistent epithelial defect, defined as a defect that has not resolved after two weeks of standard treatment, is a significant long-term management problem for ODs.[4]

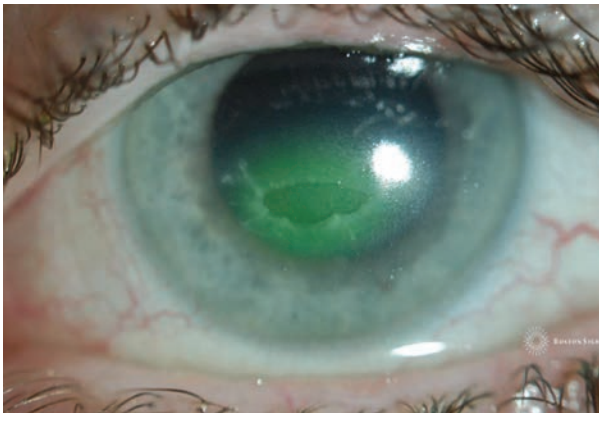


Fig. 1. Diffuse fluorescein staining with white light reveals this epithelial defect.

Some risk factors that can confound corneal epithelial healing include trauma, diabetic keratopathy, limbal stem cell deficiency, dry eye disease (DED), exposure keratopathy, neurotrophic keratopathy after penetrating keratoplasty (PKP) and herpetic infections and diabetic vitrectomy.[5] Each condition can affect the normal metabolism of the epithelium and delay, disrupt or suspend healing of an epithelial insult.

The main therapeutic goal is to provide an environment conducive for the eye to restart and complete the epithelialization process. This usually involves providing extra lubrication and supporting the ocular surface to allow for the normal proliferation and migration of differentiated epithelial cells to cover the defect.

Early intervention and resolution is key, as research shows the length of time a defect is left open is proportional to the time it will take for the defect to be fully repaired.[6,7]

Assessment

When evaluating a persistent epithelial defect, clinicians should carefully record both positive and negative pertinent findings. To properly monitor the healing process, clinicians should record the size and location of the defect at each visit and image in white light and blue light immediately after fluorescein instillation (*Figures 1 and 2*).

Clinical experience suggests the size and shape of the defect is most conspicuous immediately after fluorescein instillation; thus, measurements and photos should be taken right away. Depending on the depth of the defect, a delay of even five minutes may result in blurred margins as the fluorescein absorbs into the surrounding epithelium and underlying stroma—making the margins harder to discern.

In addition, clinicians should monitor for any change in inflammation throughout the management period by noting anterior chamber reaction for inflammatory cells and flare. Underlying or associated haze or infiltrates may be red flags for concurrent infectious activity. If all is quiet, the lack of inflammatory cells and flare can be recorded as pertinent negative findings to confirm there is no concurrent inflammatory or infectious activity.

During treatment, the patient should be evaluated frequently, even daily initially, to monitor progress.

Standard Treatments

Many factors will influence your treatment regimen, including concurrent conditions, the patient's systemic health, medication use and response to treatment. Here is a look at the treatment options available and when it's best to use them:

Address contributory factors. If an underlying infiltrate is observed with the defect, aggressive measures should be taken to treat a presumed infectious component until negative corneal cultures prove otherwise. The first priority is to treat any infectious process to prevent progression to corneal melt and perforation.[8]

In addition, many concurrent topical medications have known corneal toxicity and can negatively impact the healing process for epithelial defects.[9-11] The topical aminoglycosides gentamicin and tobramycin, for example, can cause superficial punctate keratitis in addition to delaying corneal healing.[12] Similarly, topical ciprofloxacin and the topical nonsteroidal anti-inflammatory drugs (NSAIDs) diclofenac and ketorolac can also adversely affect corneal wound healing.[13,14] In addition, commonly prescribed glaucoma medications such as latanoprost, travoprost, brinzolamide and dorzolamide cause low-grade chronic inflammation with prolonged use.[9]

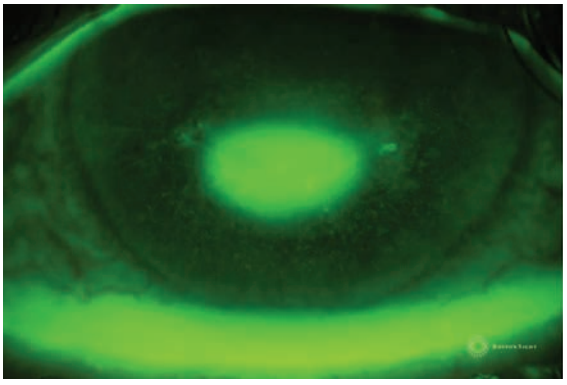


Fig. 2. Picture of an epithelial defect taken several minutes after fluorescein instillation. As the fluorescein absorbs into the stroma, the edges are obscured, making it difficult to determine its exact size and shape.

Perhaps more importantly, the ubiquitous preservative benzalkonium chloride (BAK) is a well-known ocular surface irritant. The wide use of BAK is due largely to its weak allergenic potential and high rate of antimicrobial properties. However, research demonstrates its toxic effects on the ocular surface, and some studies show significantly fewer symptoms and signs when patients use preservative-free glaucoma medications.[15,16]

Whenever possible, clinicians should modify a patient's medication use during the treatment period to decrease the effect of medicamentosa and provide an environment more conducive to corneal healing.

Aggressive lubrication. Bathing the cornea in adequate lubrication should be the first line of attack to initiate the epithelialization process. Depending on the underlying cause of the persistent defect, poor surface lubricity could be the main reason for delayed resolution. Ointment or preservative-free artificial tears should be generously applied every hour for ointment, every half hour with artificial tears. The adage "you can't use too much" certainly applies here. Ointment, though it is accompanied by concomitant visual symptoms, is the preferred modality because of the increased contact time with the cornea.[3]

Punctal occlusion. Another measure to provide a more lubricious environment for the ocular surface is punctal occlusion in the presence of dry eye syndrome. However, punctal occlusion may exacerbate any toxicity present from topical medications, and clinicians should be aware of all medications the patient is using to avoid adverse effects.[3]

Bandage soft contact lenses. The use of a silicone hydrogel contact lens can be effective in protecting

Etiologies of Persistent Epithelial Defect[3]

- Trauma and infection
- Diabetic keratopathy
- Limbal stem cell deficiency
- Severe DED
- Exposure keratopathy
- Neurotrophic keratopathy
  - Status post PKP
  - Herpetic infections
- PKP
- Diabetic vitrectomy

the underlying cornea from the shearing forces of the lid that occur with every blink. Such protection is particularly helpful for newly formed cells attempting to migrate and form a new epithelial layer. Because of the risk of infectious keratitis, these patients should be seen frequently to monitor the healing process and rule out infection. Concurrent topical preservative-free antibiotics should be prescribed for prophylaxis.

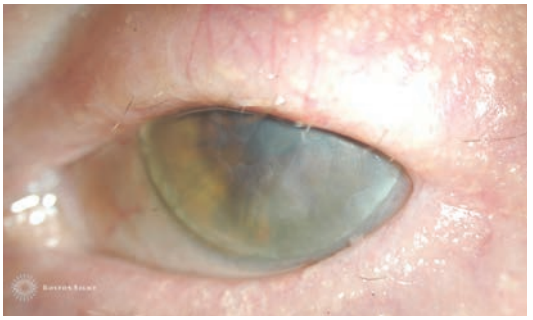


Fig. 3. This patient has a history of neurotrophic keratopathy secondary to herpes simplex keratitis. He suffered multiple episodes of surface breakdown that ultimately responded to a lateral tarsorrhaphy, which has been kept in place for surface maintenance.

Pressure patching. Though a common treatment option in the past, evidence suggests pressure patching can actually impede the healing process and be a source of infection.[17-20] Several studies show either no additional benefit or delayed healing with pressure patching compared with use of antibiotic and mydriatic alone.[19,21]

Secondary Options

In spite of many traditional treatment options, some conditions may prove to be recalcitrant and require secondary therapies:

Scleral lenses. Research suggests scleral lenses and PROSE (for "prosthetic replacement of the ocular surface ecosystem") devices (BostonSight) can be effective in the treatment and resolution of epithelial defects.[22-25] PROSE is a medical treatment model developed to treat complex corneal conditions. Treatment involves the customized fitting of ocular prosthetic devices to achieve one or more of the following goals: improve vision (particularly for irregular corneas), improve comfort (for severe ocular surface disease) and support the ocular surface (for pathology of ocular surface disease). For persistent epithelial defects, the device may help to provide an environment that is conducive to corneal surface rehabilitation by continually bathing the ocular surface and providing a mechanical barrier against the eyelid during blink related micro-trauma.[22,25]

The treatment of a persistent epithelial defect with scleral lenses or PROSE devices involves overnight wear with daily monitoring to track resolution of the defect and check for any infectious or inflammatory events. Daily wear will provide only a partial benefit, as healing improves much quicker with overnight wear. A drop of preservative-free moxifloxacin is applied, either in the eye prior to lens insertion or into the reservoir with preservative-free saline. Vault should be sufficient to clear the limbus. Based on clinical experience, the key is to fit the lens as loose as possible to reduce suction and inflammatory triggers that come from a tight-fitting lens. Typically, a larger diameter lens with adequate toricity will work better for overnight wear than a smaller lens that may have more suction. If the patient can tolerate the awareness that comes with edge lift of the peripheral curve, this would be acceptable, even preferred, to create a looser fitting lens.

Anecdotally, though longstanding persistent epithelial defects may not respond to one night of scleral lens wear, once healing is initiated after several nights, the healing rate will increase and full resolution will occur soon thereafter.

After resolution of the defect, researchers postulate that continuing overnight wear for 24 to 48 hours may reduce recurrence of surface breakdown.[22]

Amniotic membrane grafting. Since their introduction in 1995, amniotic membrane grafts have been used for many ocular surface conditions, including persistent epithelial defects.[26,27] Two types are available: cryo-preserved and epithelialized. The latter of the two needs to be maintained at -80°C and dehydrated, unless it is de-epithelialized, in which case it can be stored at room temperature.[26] Prokera (BioTissue) cryopreserved amniotic membrane is a commonly-used option that can be inserted in-office with relative ease, though some patients find the ring to be a source of discomfort. BioDOptix (BioD) and AmbioDisk (Katena) are other amniotic membrane options.

The role of amniotic grafts in re-epithelialization of persistent epithelial defects may involve a mechanical effect where the basement membrane of the graft serves as a scaffolding on which regenerating epithelial cells can migrate.[26] Researchers speculate that the basement membrane also reinforces adhesion of basal epithelial cells and promotes epithelial differentiation.[28,29] In addition, the growth factors necessary for healing are present in amniotic membrane.[30]

Autologous serum. This can be beneficial to initiating and expediting the healing of an epithelial defect because it contains the growth factors necessary for re-epithelialization.[7,31,32] Clinicians often advocate

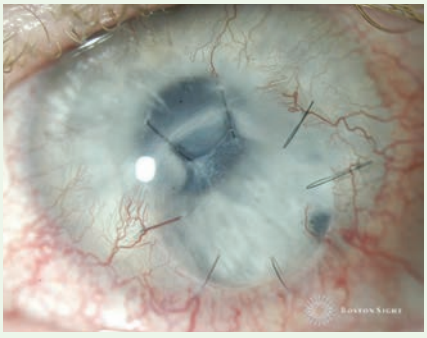
for frequent instillation, such as one drop every two hours, to expedite healing. One study found an average healing time of 22 days with the use of 50% serum drops.[7]

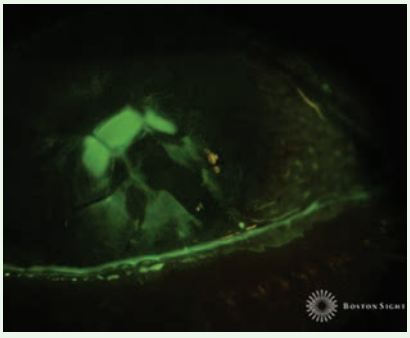
Recent evidence suggests the use of autologous serum eye drops with silicone hydrogel soft contact lenses is an effective combination therapy for persistent epithelial defects.[33-35] This protocol combines the mechanical protection of a bandage soft contact lens with the nutrients of autologous serum eye drops to provide a synergistic effect on healing. The use of autologous serum after resolution of the epithelial defect with a bandage contact lens also showed less recurrence.[33]

However, logistical obstacles to using autologous serum may limit its utility. The process of attaining the drops first requires a blood draw, which may be prohibitive for

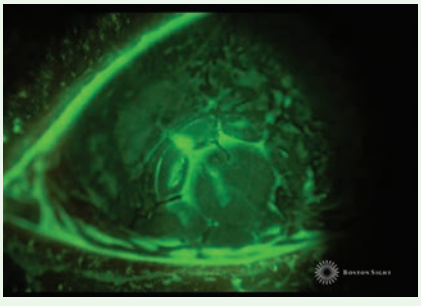
Case Example

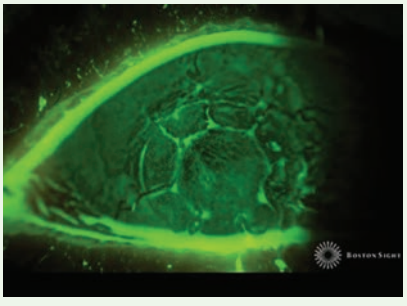
A 38-year-old Caucasian female presented with a history of systemic lupus erythematosus and Stevens-Johnson syndrome with severe ocular complications. She suffered an ulcerative keratitis in the left eye that perforated, requiring a therapeutic PKP. Postoperative assessments showed incomplete re-epithelialization of donor graft that, over a course of a month, did not respond to bandage contact lens treatment and topical gentamicin. She was referred for PROSE treatment and resolution of persistent epithelial defect.





Figs. 1 and 2. After PKP, this patient had active neovascularization to the graft-host interface. The fluorescein image highlights the persistent epithelial defect.





Figs. 3 and 4. At left, the fluorescein image after one day of overnight lens wear shows significantly less staining on graft tissue. At right, the patient found resolution of the epithelial defect after two nights of overnight lens wear.

Her entering visual acuity with correction (VAcc) was 20/30 OD, 20/400 OS. Anterior segment evaluation was significant for cauterized lower puncta OD, OS, conjunctival injection 3+ temporally and inferiorly OS, a decentered 6mm corneal graft with several intact sutures and active corneal neovascularization to the graft 360 degrees with corneal vessels at the graft-host interface infero-nasal (*Figure 1*). There was a 3mm epithelial defect 10 to 12 o'clock within graft (*Figure 2*). The PROSE treatment was initiated OS with the following device parameters: Boston XO2 (Dk: 140), 8.5mm BC, +3.50D, 19.0mm diameter and with-the-rule toric peripheral curves.

The initial device assessment showed alignment of the peripheral haptics. Prior to insertion, a drop of Vigamox was instilled into the reservoir of the device, along with preservative-free saline solution, for prophylaxis against infectious keratitis. The patient was instructed to not remove the device overnight and to return in the morning for evaluation.

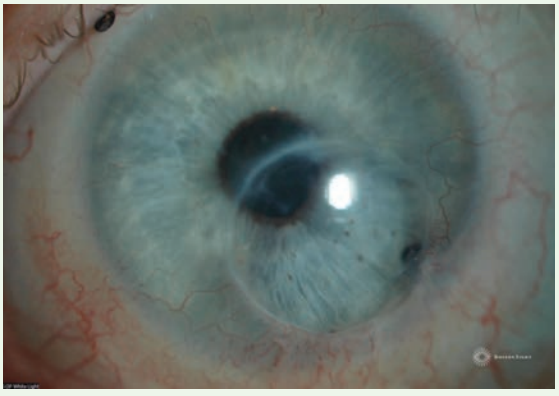


Fig. 5. The patient's left eye two years after treatment.

Follow Up

The next day, the patient's VAcc was 20/30 OD, 20/125 OS. The anterior segment evaluation showed slightly reduced conjunctival injection at 2+ OS and a significantly reduced epithelial defect on the graft (*Figure 3*). By the next day after another night of overnight wear, the defect was resolved (*Figure 4*).

Overnight wear of the device was discontinued and erythromycin ointment was prescribed prior to bedtime for overnight lubrication. The patient continues to wear the PROSE device on a daily basis and has had no recurrence of epithelial breakdown. At a recent visit, the eye was white and quiet with ghosted corneal vessels that were previously active (*Figure 5*).

patients with limited access to care or who are disabled.

Limbal stem cell transplantation. This is an advanced option when other standard and secondary therapies fail for patients with limbal stem cell deficiency as a complicating factor. The procedure involves the transplantation of limbal stem cells to the affected eye.[36] The source of the grafted tissue can be either an autograft from the contralateral eye or allograft from a donor. Autologous transplantation of tissue from the contralateral eye will ensure no graft rejection, although the grafted eye may be susceptible to limbal stem cell deficiency.[3]

Tarsorrhaphy. When other options are unsuccessful or are unavailable, temporary partial or complete tarsorrhaphies can be effective in providing an environment conducive to healing (*Figure 3*). This is a good option when exposure keratopathy is either contributory to the formation of the defect or may complicate healing. Clinicians should also consider this treatment modality for patients who are noncompliant or are physically unable to apply lubrication drops.[3]

Despite myraid treatment options, persistent epithelial defects remain challenging entities for even the most seasoned clinician, and patience is a key virtue. Clinicians must be vigilant with follow up and see the patient daily or every other day until resolution, and the timeline depends on the obstinacy of the disease and the effectiveness of the treatment. Some defects may respond fairly quickly (i.e., one to two days with overnight scleral lens wear) or may be more prolonged over several weeks. Once healed, clinicians should ensure patients have sufficient lubrication and manage medicamentosa to reduce the likelihood of recurrence. In most of these vulnerable patients, recurrence of surface breakdown may be common and warrants more frequent examinations beyond the annual visits. ■

Dr. Kwok is a clinician at BostonSight and was previously a faculty member of the New England College of Optometry specializing in contact lens education. He is a graduate of the University of Waterloo School of Optometry and completed a primary care residency at the New England College of Optometry.

Therapies in the Pipeline

Other treatments in development are promising:

Matrix regenerating agent. Recently available in Europe, this is a large biopolymer that is an analog of glycosaminoglycan integral to the structure of the extracellular matrix. Research demonstrates topical application effectively heals persistent epithelial defects after fortified antibiotic treatment of bacterial keratitis.[37]

Amniotic membrane extract. Research is being conducted on a lyophilized preparation of amniotic membrane that can be used as an eye drop.[2,36] The presence of growth factors in this extract could potentially have similar efficacy in healing of amniotic membrane in topical form the patient applies at home without the need for in office-application.

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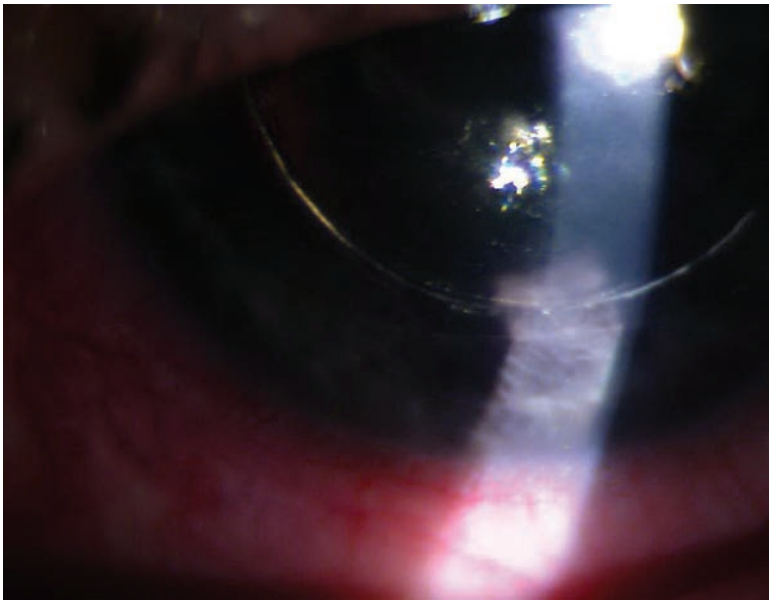
AN OD'S GUIDE TO Corneal Transplant OPTIONS

Optometrists can play a significant role in preparing patients for these procedures and safeguarding against complications. By Mitch Ibach, OD, and Scott Hauswirth, OD

To preserve patients' vision and ocular health, primary eye care providers need to stand confidently alongside ophthalmologists to assist in postoperative management. With respect to corneal pathology, restoring vision can now be achieved, in some cases, by applying corneal transplants using less risky, more predictable procedures.

As transplant procedures become safer and more precise, more are performed both in the United States and worldwide.[1] According to the Eye Bank Association of America, 79,304 keratoplasties were performed in 2015, an increase of 3.75% from 2014.[1]

As optometrists managing corneal disease, our job is to be well-versed in cornea transplant options, educate the patient, make the appropriate referrals and actively participate in patients' postoperative care.



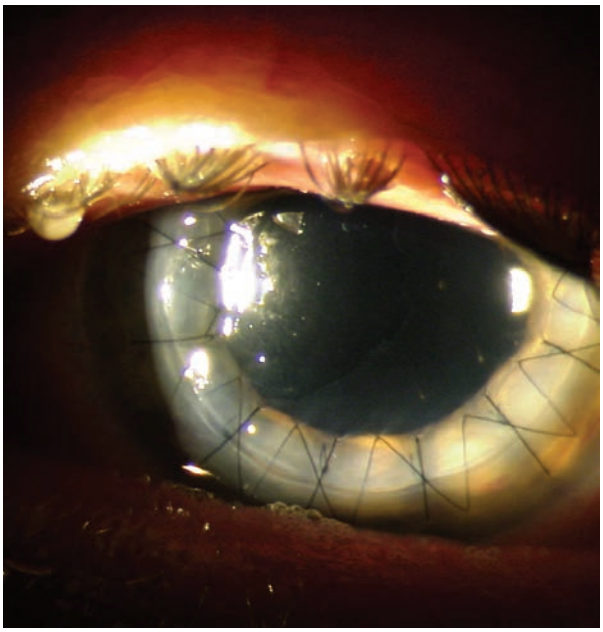
DSEK with gas/air bubble posterior to the iris causing pupillary block.

The term *corneal transplant* is no longer synonymous with full-thickness penetrating keratoplasty (PKP). It is now divided into subcategories with different tissue layers. This family of procedures includes traditional PKP, deep anterior lamellar keratoplasty (DALK), Descemet's stripping endothelial keratoplasty (DSEK/DSAEK), Descemet's membrane endothelial keratoplasty (DMEK) and pre-Descemet's endothelial keratoplasty (PDEK).

This article reviews these options, what patients need to know and the optometrist's role in comanagement.

Penetrating Keratoplasty

A traditional PKP involves the removal of all cornea layers, which essentially leaves the globe open for a period of time (called an "open sky" procedure) until the donor tissue can be secured. Next, the donor graft is attached using four interrupted cardinal sutures, secured sequentially 180 degrees from one another, ensuring proper tension on the graft to minimize induced astigmatism. Next, either more interrupted sutures are placed in the primary clock hours or, in

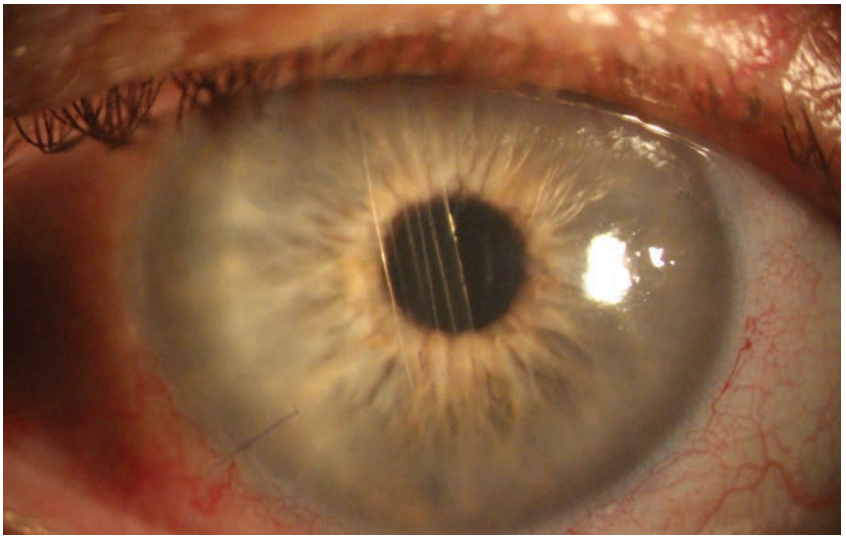


This postoperative patient demonstrates full-thickness penetrating keratoplasty graft with a running suture in place.

some cases, a long, single running suture is placed in a circumferential fashion to assist in securing the donor tissue to the host. Some surgeons prefer placement of a combination of interrupted and running sutures.

The advent of femtosecond laser technology has made a significant impact on the world of anterior segment surgery—from the creation of LASIK flaps to employment in cataract surgery for precutting the capsulorhexis and "prechopping" the lens prior to phacoemulsification. During corneal transplants, a femtosecond laser may also be used in place of the corneal trephine to create the initial incisions into the host cornea, as well as cutting of the donor button. The graft-host junction may be manipulated and customized to a specific architecture, theoretically providing a more secure interface with greater surface area.

In a procedure as invasive as a full-thickness PKP, suprachoroidal hemorrhage is an intraoperative risk. The incidence of this complication ranges from 0.1% to 1.08%.[2] If the eye is not closed quickly, total prolapse of the contents of the eye may occur, resulting in complete vision loss.[2] Postoperative PKP risks include retinal detachment, endophthalmitis, glaucoma, cataract, ocular surface disease, infectious keratitis, graft dehiscence, graft failure and graft rejection.[3]



As opposed to the pristine DMEK patient (at right), you can see this detached DMEK is rolled up in the patient's anterior chamber.

PKP Postoperative Care

Following the procedure, medications include topical immunosuppression, antibiotic coverage and lubrication in support of the ocular surface. Common corticosteroids following PKP include prednisolone acetate 1% and Durezol (difluprednate, Novartis). Typically, these medications are maintained for several months to years following surgery to modulate the recipient's immune response to graft tissue. These topical drugs may be supplemented by systemic immunomodulatory agents such as CellCept (mycophenolate mofetil, Genentech) in patients at high risk for graft rejection.[4]

A typical graft appearance on day one will show moderate graft edema throughout the donor tissue and the margins of the host rim. In the first few weeks following the procedure, control, tissue integrity maintenance and ocular surface recovery are the focus. Patients may also have a wide variety of pain from persistent foreign body sensation to more intense aching, soreness and photophobia. Generally, these symptoms improve over the first few days. Persistent or increasing inflammation over the first few days, especially in association with anterior chamber reaction or presence of hypopyon, may indicate infection.

As the new cornea stabilizes over the first two to four weeks, vision will gradually improve. You may encounter issues such as high or irregular astigmatism. In eyes that do not show improvement of edema and vision, monitor for signs of primary graft failure.[5]

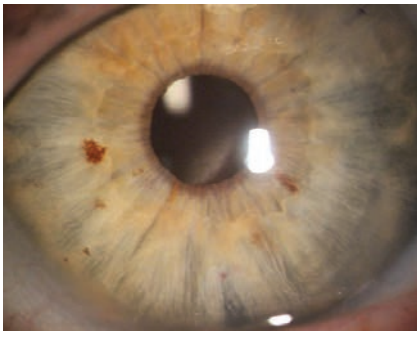
Endothelial rejection is a leading cause of graft failure.[5] Symptoms of this will include redness, photophobia, pain and blurred vision.[5] The clinical signs of a graft rejection include decreased acuity, conjunctival hyperemia, corneal edema, subepithelial infiltrates and keratic precipitates, often in a pathognomonic pattern called a Khodadoust line.[5]

Risk of graft rejection is increased with corneal neovascularization, and researchers have tested drugs to help minimize the vascular ingrowth. One study shows complete regression of deep stromal vessels in 16 patients using Avastin (bevacizumab, Genentech), partial regression in six and improved visual acuity in five.[6] Researchers have looked into in various delivery methods for Avastin, including topical, subconjunctival and intrastromal injections.[6]

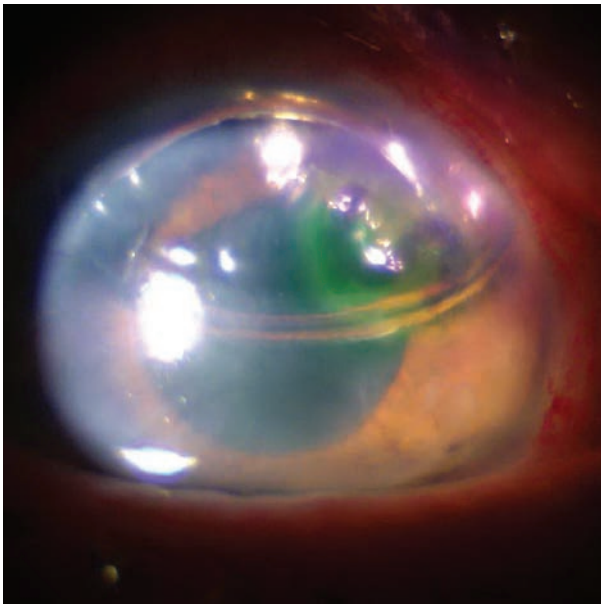
Lamellar Keratoplasties

The goal of all posterior lamellar keratoplasties is to remove the diseased endothelial pump cells while leaving unaffected layers intact. Healthy endothelial cells are critical for stromal deturgescence and corneal clarity. These transplants offer improved quality of vision and ocular health to patients with endothelial diseases such as Fuchs' dystrophy and pseudophakic bullous keratopathy.[7] These transplants also offer the advantage of keeping more native anatomy in place, decreasing the antigenic burden of foreign donor tissue.

In DSEK, the surgeon removes the host Descemet's membrane and endothelium before inserting a donor graft of posterior stroma, Descemet's and endothelium. The incision—through which the graft is inserted—is larger and is closed by the surgeon with one dissolvable suture. Finally, an air or sulfur hexafluoride (SF_6) gas bubble is inserted into the anterior chamber and the patient is positioned with their nose pointed to the ceiling, capitalizing on gravity



This is how a pristine post-DMEK patient should appear.



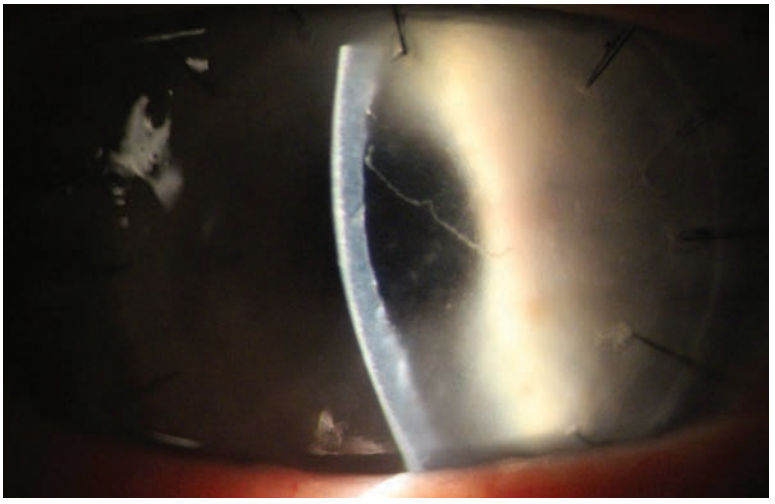
This photo shows a one-day postoperative DSEK patient with bubble in place.

to tamponade the graft into place. Topical steroids are used to maintain graft clarity and prevent rejection episodes. Steroids dosed four times per day in the early postoperative period is common, then tapering down over one year.

Postoperative complications can be segmented into two stages: *early* (one to 28 days postoperatively) and *late* (28 days and later). In the early stage, adverse events include problems with graft adhesion and iatrogenic pupillary block secondary to the anterior chamber. We typically instruct patients to maintain a supine position as often as possible after the procedure to maximize the tamponade effect of the air bubble on the graft position.

An inferior peripheral iridotomy (PI) is placed in endothelial keratoplasties (EK), but if the bubble is blocking the PI, the iridotomy is non-patent or the bubble moves posterior to the iris causing chamber shallowing, iatrogenic pupillary block with a sky-high intraocular pressure (IOP), headache and nausea/vomiting can ensue.

Symptoms of pupillary block are similar to acute angle-closure glaucoma and include headache, nausea, blurred vision and halos.[8] You can initiate a simple intervention when these patients first call the office by having the patient sit up, a position that will cause the air bubble to rise. If in 20 minutes to 30 minutes the patient experiences no relief, they must be seen. During an office visit, a corneal surgeon will



Khodadoust line and corneal graft rejection as seen in a PKP patient.

manipulate the bubble with a partial removal through the corneal wound or paracentesis (similar to "burping" a wound). Once the bubble diffuses out of the anterior chamber (approximately four to seven days after the procedure) EK grafts should attach to the host tissue. In instances when they don't, the surgeon may opt to place a second air bubble at the slit lamp with subsequent patient positioning. In rare cases, the surgeon may need to refloat the graft in the operating room or consider a graft exchange if graft attachment is unlikely through in-office manipulations. Once the problem has been resolved, the patient needs to be monitored carefully until the gas bubble has dissolved and they are no longer at risk.

In all these procedures, it is critical to monitor IOP at each visit because the patient will be on steroid therapy for an extended period. If IOP increases in the short term, use a topical IOP agent such as Combigan (brimonidine/timolol, Allergan) or Simbrinza (brinzolamide/brimonidine, Novartis) to decrease ciliary body production while the steroid is tapered. Cosopt (dorzolamide/timolol, Akorn) is also an option.

Dealing With Rejection

Late-stage complications and management involve restoring visual acuity and preventing graft rejection or failure. In comparison with PKP, DSEK offers fewer corneal sutures and more native anterior corneal tissue, resulting in less total astigmatism.[9] Generally, the thinner the transplant tissue and the more host anatomy left in place results in better acuity and less risk of graft rejection.[9,10] A review of DSEK found astigmatic shift post-DSEK to be near neutral at 0.11D.[9] Clinically, less induced astigmatism coupled with a thinner graft offers faster recovery and better potential visual acuity in DSEK patients when compared with PKP.[9-11]

If a rejection episode does occur, treat aggressively with strong topical steroids such as Durezol (difluprednate, Novartis) or Pred Forte (prednisolone acetate, Allergan) dosed up to every hour as first-line treatment.

Comparing Techniques

Research suggests DSAEK does better than PKP when it comes to risk for rejection.[12] A five-year survival study of DSAEK vs. PKP in a large cohort of Asian eyes with Fuchs' dystrophy and bullous keratopathy shows statistically significant differences in graft survival, endothelial cell loss, graft rejection and wound dehiscence.[12] Another study shows that outcomes were stronger for patients who had a failed PKP and underwent a second full-thickness keratoplasty than for patients whose doctors replaced only the diseased posterior layers of the failed transplant.[13]

DMEK is an even thinner transplant for patients with endothelial disease. In DMEK, the surgeon removes the patients Descemet's membrane and endothelium and inserts a donor button of Descemet's membrane and endothelium. Similar to DSEK, one dissolvable suture is placed and an air or sulfur hexafluoride gas bubble is used for graft tamponade. Again, in DMEK a postoperative steroid is used to maintain transplant health, tapering over one year without stopping. In our clinic, the steroid is tapered over one year before stopping with the same guidelines for graft rejection episodes occurs.

The visual acuity achieved with DMEK is generally superior to DSAEK.[7,11,14] This may be due in part to DMEK's use of a thinner graft with more native corneal anatomy, less induced hyperopia and less induced higher-order aberrations.[7,11,14]

A disadvantage of DMEK, however, is graft dislocations. The literature documents higher graft re-bubble rates compared with DSEK.[7] Researchers suspect better graft adhesion in DSEK is due to additional stromal tissue from the graft.[7]

Lastly, PDEK involves Dua's layer. This graft is similar to DMEK with an additional 10µm to 15µm anterior to Descemet's membrane. This new approach is not widely performed or studied thus far. but the hope is this variation provides the benefits of both DMEK and DSEK.[15]

Corneal transplant surgery has undergone several changes throughout the years and continues to evolve alongside innovations in technology. The movement towards lamellar grafts and replacing only the diseased tissue instead of the entire cornea has been beneficial for graft survival, as well as recovery times and improved visual outcomes for patients. As primary eye care providers with increasing patient demands, it is imperative that we comanage corneal transplantation when necessary and can make appropriate referrals for our patients to achieve optimal outcomes. ■

Dr. Ibach specializes in advanced anterior segment surgery care and pathology at Vance Thompson Vision in Sioux Falls, SD. He is a fellow of the American Academy of Optometry and a member of the American Optometric Association. He has a consulting agreement with Alcon.

Dr. Hauswirth is a practicing optometrist at Minnesota Eye Consultants and an adjunct clinical faculty at Southern California College of Optometry. He is an active industry consultant and speaker. Relevant disclosures: Alcon, Allergan, Bausch+Lomb, BioTissue, Shire, Sun and TearScience.

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Intruder Alert: Diagnosing Corneal Infiltrative Disease

The age-old question, "is this sterile or infectious?" may be an oversimplification. This review will help you find the underlying cause of your patient's issue.

By Suzanne Sherman, OD, and Fiza Shuja, OD

Conquering corneal infiltrates is something clinicians have attempted to do for decades. Despite continued research and elevated clinical acumen, if you were to put 20 clinicians in front of 20 slit lamps and ask them to properly distinguish between sterile and infectious corneal infiltrates (whether bacterial, viral, fungal or protozoan), you would hear many differing opinions.

Perhaps that is because the question itself is inherently flawed—an infiltrative process accompanies every infection. Likewise, a loss of stromal substance in corneal ulceration is often (but not always) accompanied by an infectious process. Some infections (e.g., fungal or protozoan keratitis) have an intact epithelium even though an infectious process is at play. Therefore, both infiltrates and ulcers can be either sterile or infectious. While it is true that diffuse infiltrates with little to no epithelial involvement are commonly sterile, clinicians need to avoid over-reliance on the rule of thumb that ulceration signifies infection and infiltrates do not.

Fig. 1. These subepithelial infiltrates are a hallmark sign of EKC.

Instead, optometrists must rely on patient history, symptoms and clinical presentation when determining the type of corneal infiltrate. Once we know what we are dealing with, only then can we choose the proper treatment and management regimen. Here is a look at the processes that lead to infiltrates and how to distinguish the various types you will encounter in your practice.

How it All Begins

Corneal infiltrates represent an immune response to corneal insult, whether from a microbial antigen, contact lens wear or even corneal surgery. A firm grasp of corneal mechanics is a first important step toward understanding how an infiltrate occurs.

The cornea, devoid of blood or lymph vessels, relies on cellular and molecular properties within it and the surrounding tissue.[1] Corneal epithelial cells are an important asset in activating the immune response. As the first line of defense, corneal epithelial cells identify an invading pathogen or other corneal insult and release cytokines and chemokines to begin the immune defense. In

addition to epithelial cells, a variety of other players are also key in the corneal defense mechanism, including keratocytes, interferons, neutrophils, natural killer cells and macrophages.[2] The active immune response involves immune cells arriving to repair the corneal damage, eventually leading to the aggregation of white blood cells in the cornea—known as an infiltrate.[3]

Although every infection has an infiltrative process, not every infiltrate is infectious. One of the important distinguishing factors between sterile and infectious infiltrates is the status of the epithelium. With an intact epithelium, more often the infiltrates are sterile; with an infectious etiology, a defect is usually present (*Table 1*).[4] The most important information needed to diagnose infiltrative events arises through patient history and presentation (*Table 2*).

Table 1. Sterile Infiltrates vs. Infectious Infiltrates[4]

Sterile	Infectious (MK)
• Smaller lesion (<1mm) • More peripheral • Minimal epithelial damage (defect size compared with underlying infiltrate) • No mucous discharge • Less pain and photophobia • Little or no anterior chamber reaction • No lid involvement	• Larger lesion (>1mm) • More central • Significant epithelial defect (size of staining defect closely mirrors size of underlying stromal lesion) • Mucopurulent discharge • Pain and photophobia • Anterior chamber reaction • Lid edema, tear film debris, hypopyon

Infections: The Usual Suspects

Although patient history and presentation will provide a better understanding of the initial antigen causing the infiltrate, it is best to proceed with caution in diagnosis and treatment.

Because it is difficult to clearly differentiate between a benign, self-limiting corneal insult and an infectious event, clinicians should first treat all infiltrative events as infectious in nature.[5] Any number of different infectious etiologies may be at play, and knowing what you are looking at is crucial. Let's review the most common infectious causes of corneal infiltrates.

• ***Viral subepithelial infiltrates.*** Adenoviruses—including epidemic keratoconjunctivitis (EKC), herpes simplex virus (HSV) and herpes zoster (HZO)—can have significant corneal involvement. Some patient history questions that can help narrow the diagnosis include whether they feel fatigued and if they had an upper respiratory infection recently.

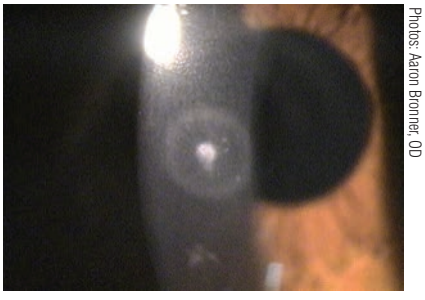
• ***EKC.*** This often presents bilaterally, and patients sometimes have a history of respiratory tract infections. Around one week to 10 days after inoculation, patients may develop follicular conjunctivitis, petechial hemorrhages, prominent preauricular adenopathy, occasionally pseudo- or true membranes and, often, associated punctate keratitis. These patients commonly complain of tearing, light sensitivity, pain and foreign body sensation. Seven to 14 days after their initial eye symptoms, patients may develop multifocal subepithelial (anterior stromal) corneal infiltrates (*Figure 1*). These become quite apparent on slit lamp examination and can range from a few to many.[6]

The punctate erosions (keratitis) arise due to adenovirus replication within the corneal epithelium, whereas the infiltrates are due to an immunopathologic response to a viral infection of keratocytes in the superficial corneal stroma. Patients who complain of photophobia and decreased vision as a result of the SEIs often have symptoms that persist for months after the initial presentation.[6]

In the case of EKC, laboratory testing is rarely indicated. However, a viral culture may differentiate between EKC and a herpes simplex virus (HSV) infection.

• ***HSV and HZO keratitis.*** These are the most commonly known viral keratitis infections other than EKC. Patient history questions pertaining to previous infections such as chicken pox, inordinate stress or recent sun exposure are helpful to identify this etiology.

HSV comes in various forms that can affect different layers of the



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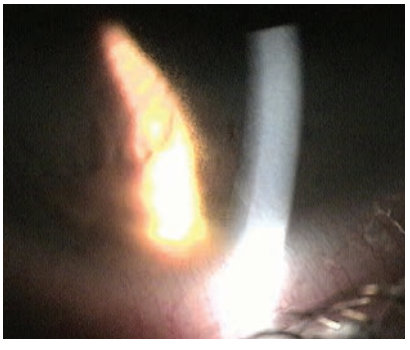


Fig. 2. Above, this infiltrate, known as a Wessely ring, was caused by a bacterial source. Below, the migrating stromal white blood cells, seen as an area of granularity on the edge of retro beam, are a response to the infiltrate above.

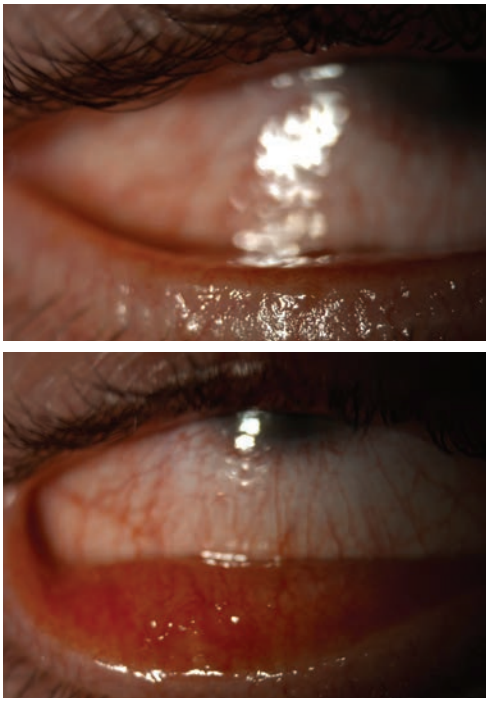


Fig. 3. Severe meibomian gland dysfunction with telangiectatic vessels.

cornea, ranging from epithelial, neurotrophic, necrotizing stromal and endotheliitis. Epithelial keratitis can present with blepharoconjunctivitis—macropunctate epithelial lesions that progress to dendritic ulceration with terminal end bulbs.[7] Anterior stromal haze can develop "ghost dendrites" below the epithelial lesions. HSV can also have a non-necrotizing and necrotizing stromal keratitis. This appears differently than a small infiltrate, as there is a central disc of stromal or epithelial edema, keratic precipitates and endothelial folds. Associated signs also include anterior uveitis, decreased corneal sensation and elevated intraocular pressure.[8]

HZO may present with epithelial keratitis comprised of small, non-ulcerated pseudodendrites without terminal bulbs.[7]

• ***Bacterial keratitis.*** This can involve a suppurative corneal infiltrate with an overlying epithelial defect after a bacterial corneal insult (*Figure 2*). The ocular flora is home to both *Staphylococcus* and *Streptococcus*, the most common agents found in opportunistic infections due to ocular surface trauma (e.g., corneal abrasion, surgery, severe ocular surface disease). In contact lens wearers, however, bacterial keratitis is most often due to *Pseudomonas*.[9,10] Although contact lens infiltrates are usually thought to be "sterile," on culture they can be either sterile or infectious; thus, infiltrates in a patient who wears contact lenses should be treated as infectious until proven otherwise.[9]

Table 2. Clinical Characterization of Corneal Infiltrative Events with Soft Contact Lens Wear[11]

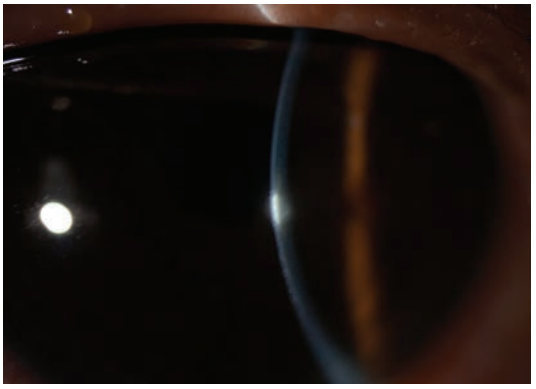
Classification	Categories	Signs and Symptoms
Serious and symptomatic	Microbial keratitis	• Infection of the cornea with excavation of corneal epithelium, Bowman's layer and stroma with infiltration and necrosis of tissue. • Focal infiltrates usually larger (>1mm) and irregular with small satellite lesions and significant diffuse infiltration. • Severe limbal and bulbar redness. • Rapid onset of moderate to severe pain, decreased visual acuity, mucopurulent or purulent discharge, tearing, photophobia and puffiness of lids.
Clinically significant and symptomatic	Contact lens-induced acute red eye (CLARE)	• Small multiple focal infiltrates and diffuse infiltration in the mid-periphery to periphery of the cornea. • Moderate to severe circumferential redness. • Moderate pain, tearing and photophobia soon after waking.
	Contact lens peripheral ulcer (CLPU)	• In active stage: focal excavation of the epithelium, infiltration and necrosis of the anterior stroma. • Small (up to 2mm), single, circular focal infiltrates. • Limbal and bulbar redness. • Severe to moderate pain, foreign body sensation. • Could be asymptomatic.
	Infiltrative keratitis	• Anterior stromal infiltration, with or without epithelial involvement, in the mid-periphery to periphery of the cornea. • Small infiltrates, possibly multiple. • Mild to moderate irritation, redness and occasional discharge.
Clinically non-significant and asymptomatic	Asymptomatic infiltrative keratitis	• Infiltration of the cornea without patient symptoms. • Small focal infiltrates (up to .4mm). • Could be associated with punctate staining. • Could have mild to moderate limbal and bulbar redness.
	Asymptomatic infiltrates	• Infiltrates in the cornea without other patient signs or symptoms.

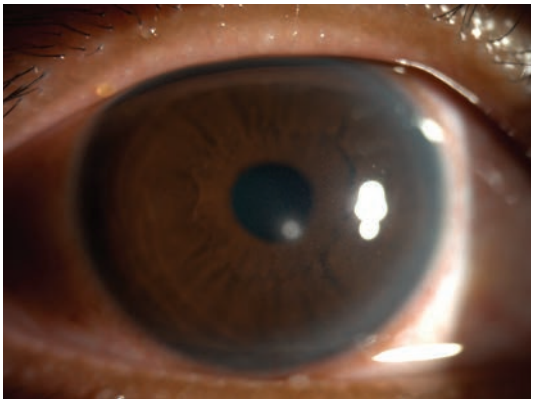
Bacteria often reside in contact lens cases, patient's hands, eyelids and in tap water; basically any entity that comes in contact with the lenses can cause a bacterial infection.[11] The antigens are trapped between the contact lens and cornea, remaining on the cornea longer due to slow epithelial cell renewal.[12] The benefit with rigid gas permeable (GP) lenses is the increase in tear exchange vs. soft lenses, which have 10 to 20 times higher incidence of infiltrative events.[10,12] GPs are also considerably more deposit resistant, reducing a key predisposing factor for infection.

Asking contact lens patients about wear time and lens hygiene are important points in the history, as these two are commonly associated with bacterial infections from contact lens wear.[12] Extended contact lens wear carries a 43% risk of bacterial keratitis.[12] Hypoxia because of overnight wear, extended wear or hypersensitivity to lens material triggers the inflammatory response, leading to the formation of an infiltrate. The infiltrate is irregular with surrounding corneal edema, and is usually described as greater than 1mm, with the possibility of adjacent satellite lesions.[11,12] A deep corneal defect extending from the epithelial layer into the stroma with necrotic tissue is also present. The infiltrate is usually located in the central or paracentral cornea.

With a *Pseudomonas* infection in particular, a large central defect can be present.[9] Symptoms often include severe pain, severe redness, photophobia, hypopyon, marked anterior chamber reaction, mucopurulent discharge and decreased visual acuity.

• ***Fungal keratitis.*** This is less common than bacterial keratitis.





Figs. 4 and 5. Central corneal infiltrates from contact lens wear.

It represents around 5% to 10% of corneal infections in the United States. The leading cause of fungal keratitis is trauma to the cornea with plant or vegetable material; however, contact lenses are another risk factor. Clinicians should ask patients about their recent activities outdoors in addition to their contact lens habits.[13]

These infections usually present with fewer symptoms than bacterial keratitis, but a deep stromal gray-white dry infiltrate with a feathery margin may be present. If the infiltrate is extremely deep, it is possible to have multifocal or satellite infiltrates, endothelial hypopyon or both. It is very important to distinguish this type of infiltrate from other forms, as topical corticosteroids are a significant risk factor. They can activate and increase the virulence of the fungal organism, which results in a decrease in resistance to the infection.[13]

• ***Protozoan infections.*** The parasitic infection we hear most about in eye care is *Acanthamoeba*. Diagnostic delay is common because of the nonspecific presentation. Presenting symptoms are often severe ocular pain and photophobia. In the early stages, a localized infection may appear in a mildly symptomatic patient with diffuse punctate epitheliopathy or dendritic epithelial lesion. A gray-white superficial infiltrate may occur in the central cornea. This infection can progress into a partial or complete ring infiltrate. It is important to question these patients if they have worn their contact lenses in a pool, hot tub or fresh water source. A diagnosis can be made by using a stained smear or by culturing organisms from the corneal scraping. Most cases are diagnosed by clinical presentation or confocal microscopy.[13]

Non-infectious Infiltrates

If you have ruled out an infectious etiology, be on the lookout for several sterile infiltrative events: You should begin by examining the company the infiltrate keeps—lid margin disease and blepharitis are often found in conjunction with non-infectious infiltrates.

• ***Marginal corneal infiltrates.*** These are caused by non-infectious conditions. Although the complete pathological process of these infiltrates is still not fully understood,

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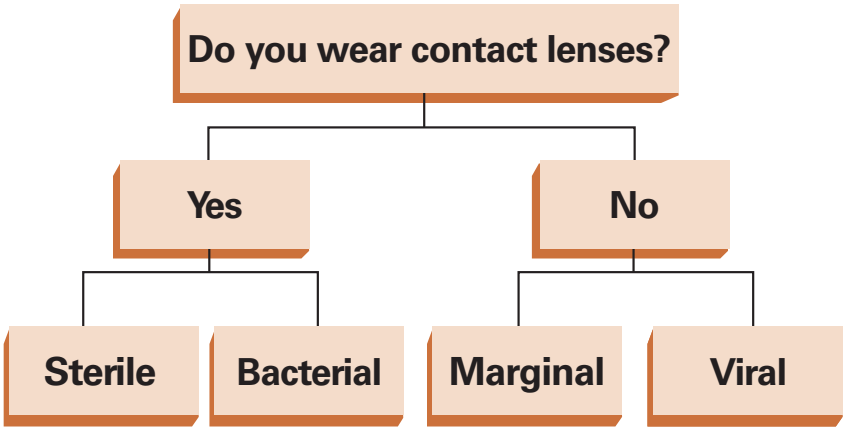


Fig. 6. While this grid is a simplification for categorization of an infiltrative event, it functions as a good starting point in identifying the infiltrative cause.

researchers do know that *Staphylococcus* grows on the eyelids and spills bacterial byproducts onto the corneal surface, beginning a hypersensitivity reaction thought to lead to infiltrates.[14]

The introduction of an antigen onto the cornea surface will cause a release of inflammatory mediators to the peripheral cornea, leading to vasodilation. The corneal limbus is very important in immune-mediated corneal disorders because it has antigen-presenting cells (APCs), such as Langerhan cells, that express major histocompatibility complex class II antigens, which are capable of efficient mobilization and induction of B- and T-cell responses. This is why immune-mediated corneal changes occur at peripheral locations adjacent to the limbus.[15]

These sterile corneal infiltrates are often small, gray-white circumlimbal lesions separated from the limbus by a 1mm clear space. The location of these infiltrates is due to the APCs that are capable of mobilization of the T-cell response. In addition, the posterior limbus is vascularized, circulating immune cells and complexes near the terminal capillary loops, causing a variety of immune responses in the corneal periphery.[15] If the infiltrates are due to chronic Staphylococcal lid disease, superficial blood vessels may occur across the clear interval between the limbus and the infiltrates (*Figure 3*).[15] They more commonly appear individually, but can appear in groups or bilaterally.[16] Infiltrates may be non-staining or have early overlying staining, and are usually present where the eyelid margin intersects the corneal surface (i.e., at the 2 to 10 o'clock and 4 to 8 o'clock areas).[15]

Slit lamp exam may also reveal mild quadrant-specific conjunctival hyperemia, little or no chemosis, trace or mild ocular irritation and normal vision. These infiltrates are self-limiting and usually disappear within one to two weeks.[15]

Clinicians should always be on the lookout for masqueraders as well. Krachmer's spots, for example, are a type of sterile infiltrate that can be mistaken for either marginal or viral subepithelial infiltrates.[17] These are a sign of subepithelial corneal graft rejection after penetrating keratoplasty, and patients may present asymptomatically. Research has yet to determine if the lymphocytic cells arise from donor keratocytes or the donor epithelial cells. These infiltrates can be accompanied by an anterior chamber reaction. If infiltrates are seen in a post-corneal transplant patient, it is important to rule out subepithelial rejection.[10]

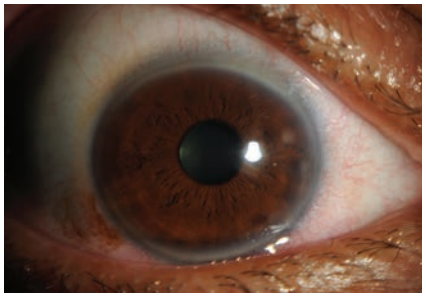
• ***Contact lens-induced infiltrative events.*** Infiltrative events can also be specifically associated with contact lens use (*Figures 4 and 5*). A lens wearer's habits will help clinicians better understand the possible cause of an infiltrative event. Proper follow-up questions include: Which type of lens? How often? For how many hours? Are you practicing appropriate lens hygiene? Do you sleep in them? Do you change them regularly? What solution do you use? Do you swim in them? With the appropriate questions during patient history, a diagnosis, such as *Acanthamoeba*, should begin to form (*Figure 6*).

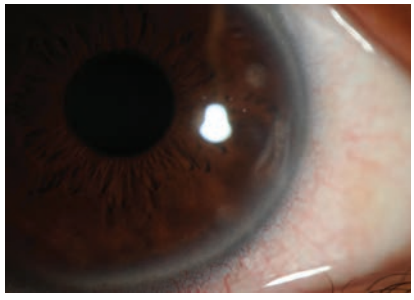
• ***Contact lens-induced peripheral ulcer (CLPU)*** is a sudden corneal inflammatory response after contact lens wear that presents with moderate-severe limbal and bulbar redness (*Figures 7 and 8*).[5] A small circular subepithelial infiltrate is often present in the periphery or mid-periphery as well (0.1mm to 1.2mm in diameter).[5] There is an associated epithelial defect with surrounding infiltrates. Presenting symptoms can include moderate-to-severe pain, foreign body sensation and irritation, or patients may present asymptomatically.[11] CLPU is self-limiting and will resolve after discontinuing contact lens wear. There can be recurrences with contact lens wear; however, proper lens hygiene is stressed to prevent further inflammation.

• ***Contact lens-induced acute red eye (CLARE)*** also an inflammatory

reaction of the cornea, often occurs after sleeping with lenses overnight. Patients will present with pain upon awakening, photophobia and tearing.[11] Multiple focal infiltrates of 1mm in diameter or less can be present in the mid-periphery or periphery of the cornea.[13] There is minimal staining and no epithelial defect present on examination.[18] Resolution typically occurs quickly after lens removal.

• ***Infiltrative keratitis.*** This condition is an inflammatory reaction with infiltrates occurring in the anterior stroma. An epithelial defect can be present, but is not a certainty. Infiltrates are located in the corneal mid-periphery or periphery and are smaller in size, usually less than 1mm in diameter.[18] Patients may present with symptoms of irritation and redness.[11] Infiltrative keratitis can also occur with asymptomatic patients, where smaller infiltrates, 0.4mm in diameter, are present in the corneal periphery.[11] Punctate staining may be present with mild redness, which differentiates this from asymptomatic infiltrates. As opposed to CLPU and CLARE, this occurs during the day and the focal infiltrates are irregular.





Figs. 7 and 8. Contact lens-induced peripheral corneal infiltrates.

Differentiation is Key

Classifying infiltrates as sterile or infectious is a challenging task, and differentiating their underlying etiologies can be complicated due to the multiple potential causes and their often-overlapping signs and symptoms. Patient presentation and a thorough case history will provide crucial information needed to narrowing down the diagnosis. Once the most likely etiology of

the infiltrate has been determined, appropriate treatment can be undertaken. With infectious etiologies in particular, the case should be approached with the most up-to-date protocols for treatment or the appropriate consultation or referral. ■

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POSITIVE VISUAL PHENOMENA:
ETIOLOGIES BEYOND THE EYE

Prepare to investigate the many non-ocular events that cause patients to see flashes or bright lights. **By Sara Weidmayer, OD**

We are all familiar with positive visual phenomena and photopsias. They are generally an entopic concern: visual perceptions produced from inside the eye, from vitreous traction on the retina, for example.[1,2] However, other positive visual phenomena represent false visual images—the brain perceives them without corresponding visual stimuli.

When a patient reports any sort of bright light or flash in their vision, our first thought is often vitreous detachment, retinal break or retinal detachment. During a normal dilated eye exam, it is easy to attribute such symptoms to a migraine aura without headache (MAWH). However, the etiology of positive visual phenomena is often not intraocular, MAWH or even other benign causes. It is critical that we carefully differentiate the source of these symptoms, as positive visual phenomena may indicate serious—even life-threatening—systemic health concerns.

Photo: George T. Banyas, OD

Migraine aura often includes a scintillating, or fortification, scotoma. Often, the central scotoma is bordered by a crescent of shimmering zigzags.

A key feature to differentiate the source of a flash is laterality; a unilateral flash generally corresponds to an ocular etiology, whereas bilateral flashes are more likely at, or posterior to, the chiasm.[2] Because clinicians are already well-versed in ocular sources of flashes, this article discusses them only briefly, focusing instead on less common—but higher risk—etiologies of positive visual phenomena.

Release Date: January 2018
Expiration Date: January 15, 2021
Goal Statement: Often, clinicians assume a patient's complaint of bright lights or flashes in vision are associated with vitreous detachment, retinal break or retinal detachment. However, it is critical that ODs carefully differentiate the source of these symptoms, as positive visual phenomena may indicate serious—even life-threatening—systemic health concerns. This article discusses how to identify less common—but higher risk—etiologies of positive visual phenomena.

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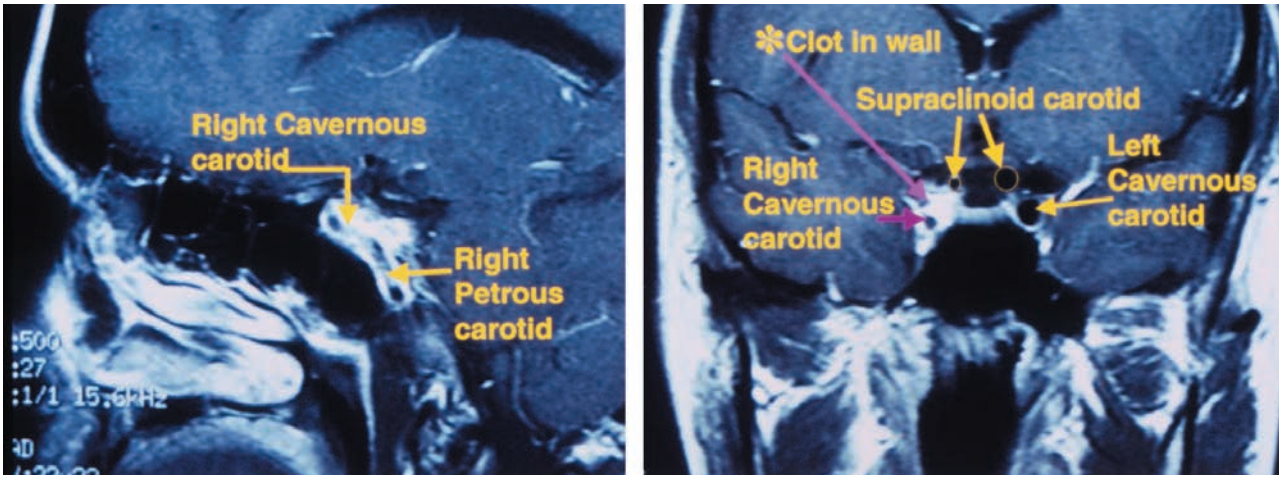


Photos: Ellen Marie Petrilla and Gina G. Wong, OD

This 36-year-old patient was complaining of constant periorbital headaches on the right side, accompanied by ptosis and miotic pupil. Four weeks earlier, she developed a temporal scintillating scotoma in her right eye that lasted 15 to 30 minutes, followed by an acute, painful headache on the right side. Sagittal MRI (left) shows an internal carotid artery dissection in the wall of the petrous and cavernous sinus segments. Coronal MRI (right) shows significant narrowing of the carotid lumen in the cavernous sinus and supraclinoid segments of the right internal carotid artery. The patient was diagnosed with a post-ganglionic right Horner's syndrome with concurrent headache and scintillating scotomas.

Ocular Sources

Many flashes can be attributed to retinal pathology, such as posterior vitreous detachment, any vitreoretinal traction or a retinal break. Any mechanical stimulation—such as tugging or compression—of the photoreceptors can trigger an entopic flash in vision.[1] In these cases, the flashes are often accompanied by floaters, such a Weiss ring, red blood cells or pigmented cells within the vitreous ("Shafer's sign") and associated fundus evaluation findings. Compression from mass effect within or onto the globe may occur from a variety of intraocular or orbital sources, ranging from choroidal lesions to orbital abnormalities such as tumors.

A thorough dilated examination should easily differentiate many of these sources of photopsia, and any signs indicating a retro-ocular compressive lesion such as proptosis, extraocular muscle motility restriction or diplopia would warrant further neuroimaging.

Photoreceptor dysfunction from inflammation or infections can also produce flashes in vision. Diseases such as progressive outer retinal necrosis, acute zonal occult outer retinopathy, retinitis pigmentosa, degenerative retinopathies or other issues that lead to photoreceptor death or dysfunction may produce a photopsia.[1] Unlike many other ocular sources of flashes, these diseases most frequently affect both eyes, though they can be unilateral or asymmetric.

Retinal vasospasm causes a focal narrowing of the retinal arteriolar lumen, effectively limiting blood flow and possibly producing a visual phenomenon in the area of relative ischemia. Although this generally would produce a negative visual phenomenon, in some cases it may be accompanied by flashing lights. Retinal vasospasms are temporary and usually recover within a few minutes.[3,4] In cases of unrecovered vasospasm, an associated visual field defect would be expected, as would an area of hypoperfusion on fluorescein angiography (FA) similar to a branch retinal artery occlusion. This diagnosis is rare and should be one of exclusion from more serious conditions such as transient ischemic attack (TIA) or cerebrovascular accident (CVA, stroke) and should be evaluated for such immediately.

Flashes or streaks of light can occur due to the positioning of an intraocular lens—known as pseudophakic dysphotopsia.[5] These often present as arcs of light in the superior temporal periphery and can be quite bothersome to patients, but are otherwise benign.

Non-ocular Etiologies

Generally, non-ocular causes of positive visual phenomena are binocular and originate from vascular- or non-vascular changes involving the cerebral cortex.

Migraine aura. This represents focal neurological symptoms that are reversible and may be seen in up to about 30% of patients with migraine.[6,7] It also accounts for most cases of bilateral positive visual phenomena.[6,8] In migraine sufferers with aura symptoms, 90% have visual symptoms.[6,8] Visual migraine aura often follows a predictable pattern: it precedes or accompanies a headache

Table 1. Features Typically Associated with MAWH, TIA, CVA and Seizure

	History	Visual Symptoms	Onset	Duration	Neuroimaging/Ancillary Studies
MAWH	History of migraine	Predominantly positive, dynamic	Gradual	Five to 60 minutes	Normal
TIA	Vasculopathic risks	Predominantly negative, static	Acute	Less than five minutes, typically; up to 24 hours	Likely ischemic cerebrovascular disease, no infarct
CVA	Vasculopathic risks	Predominantly negative, static	Acute	Less than five minutes	Area of cerebral infarct
Seizure	History of seizure or epilepsy, head trauma, vasculopathic risks	Predominantly positive, dynamic	Acute	Transient	EEG most useful

and may also present with symptoms typical of migraine, such as nausea, photophobia and phonophobia, sometimes with focal weakness, numbness or paresthesia, dizziness or dysphasia.[6,7,9] While migraine with typical aura is a straightforward clinical diagnosis, aura symptoms in the absence of headache is more difficult to discriminate from more serious etiologies such as TIA. Migraine aura is rarely a stand-alone migraine variant; this entity is known, among other names, as acephalgic migraine, optical migraine, migraine accompaniments, migraine equivalents or typical MAWH.[6,10]

Migraine aura normally starts gradually with a generally binocular, typical scintillating scotoma that subsequently intensifies over the course of five minutes to one hour, though 15% to 30% may extend beyond one hour.[6,7,11] Many patients describe its onset as a small central flashing light expanding radially to include an enlarging area of visual field; it is often arcuate, or in many cases forms a shimmering or flickering jagged circular pattern, often called teichopsia, or described as a fortification spectrum.[6,12] It usually also includes areas of negative visual features such as scotomas or hemianopia, a heat wave sensation and visual blur.[6,7,10] When the aura is associated with migraine, it is most often contralateral to the headache, but can be ipsilateral.[8] While many variations exist, a key component is the scintillating scotoma's dynamic, traveling presentation.

Typically, after visual aura comes a speech aura in about one-fourth of patients, followed by a sensory aura in about one-third of patients. While this order of aura is typical, it may vary in about 30% of patients. Motor involvement describes hemiplegic migraine. Progressing through sequential aura is consistent with the cortical spreading depression from brief cortical hyperexcitability, which is thought to cause MAWH and may be helpful in diagnosing MAWH.[13-15]

In cases where patients present with visual symptoms similar to a migraine aura, especially with any associated neurological deficits and particularly in older patients or those with cardiovascular risk factors but no history of migraine or similar previous episodes of migraine or aura, clinicians must conduct a careful case history to rule out TIA, CVA, seizure, inflammatory cerebrovascular disease and vertebrobasilar insufficiency—all of which can cause positive visual phenomena.[6,10]

The current criteria for diagnosing MAWH require at least two episodes of aura. Therefore, any inaugural episode should first be treated as a TIA, as stroke risk is highest within two days of TIA—not to mention other causes are often uncovered in a TIA/stroke workup.[7] Additionally, any aura that is less than five minutes or longer than an hour should be further evaluated for other causes.[7,16]

Of note, migraine is an independent risk factor for ischemic stroke, or migrainous infarction.[7,10,12] However, transient visual symptoms, similar to those of MAWH, are not uncommon—even later in life—and do not appear to be associated with an absolute higher stroke risk.[10]

Transient ischemic attack. TIA symptoms result from local ischemia, usually due to thrombotic or embolic vascular disease, but the TIA itself does not result in acute or permanent infarction.[11,17] TIA affects about five million people per year in the United States.[17] Ischemic stroke, on the other hand, indicates cerebral or central nervous system infarction and may either share similar symptoms with TIA or may happen without symptoms.[17]

The clinical symptoms of TIA are generally brief (a few seconds to a few minutes), and by definition there must be no infarct of the central nervous system.[7] Common symptoms include numbness, weakness, tingling or paralysis of one side of the face or body; transient monocular vision loss (amaurosis fugax); aphasia or dysphasia; and dizziness.[18] The visual symptoms are predominantly negative, present in corresponding

hemianopic fields if the affected area is chiasmal or post-chiasmal, tend to be abrupt and at maximum within a couple minutes of onset and are stationary, as opposed to the gradual and dynamic visual symptoms with migraine aura.[1,12,13] Though positive visual phenomena are less common, they can occur within an area of scotoma.[12,13,19] As with non-visual symptoms, visual manifestations usually last less than five minutes, but may last up to 24 hours.

Patients who have experienced TIA symptoms should immediately undergo neuroimaging to evaluate for CVA, preferably MRI with diffusion-weighted imaging (DWI), within 24 hours of when the symptoms began, if possible; however, acute infarcts may initially appear normal on MRI because tissue injury has not yet become radiologically significant, and some deep brain infarcts cannot be well visualized with MRI imaging. Regardless, MRI is more sensitive than CT for identifying ischemic areas, and DWI-MRI studies are even more precise than standard MRI or CT.[17] Positive DWI signals imply higher risk of subsequent ischemic events. If MRI is unavailable or contraindicated, clinicians should order a CT.[17] An assessment of the intracranial arteries is often done concomitantly (with MR or CT angiography).[20] Neuroimaging is important to identify or rule out a vascular (hypoperfusion, acute infarction, or large-vessel stenosis) or non-vascular (e.g., mass, abscess) origin of the TIA symptom.[17]

Clinicians should also evaluate the carotid arteries via noninvasive testing, such as Doppler ultrasound, as carotid stenosis is common in patients with atherothrombotic TIA or CVA. Basic TIA/CVA lab tests include complete blood count (CBC), blood chemistry panel and a basic coagulation assessment (prothrombin time, partial thromboplastin time).[17]

There is no standard for cardiac evaluation in TIA patients, but the heart can be the underlying cause of TIA and accounts for 14% to 30% of ischemic CVA; for example, atrial fibrillation and recent myocardial infarction can lead to thromboemboli, and valve stenosis can lead to calcific emboli.[21] Electrocardiograpy (ECG/EKG), cardiac event monitoring and echocardiography may be assessed if the initial evaluation did not uncover a source of the TIA symptoms; however, few patients with either no history of heart disease or with normal ECG will have a cardioembolic source for TIA.[17]

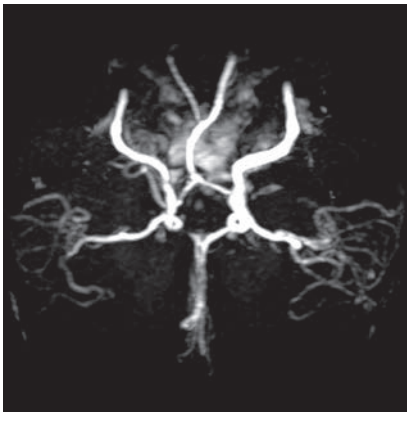
Seizures. These have a number of causes, including developmental malformations, ischemia or infarction, compressive lesions or trauma; they may also be idiopathic.[13]

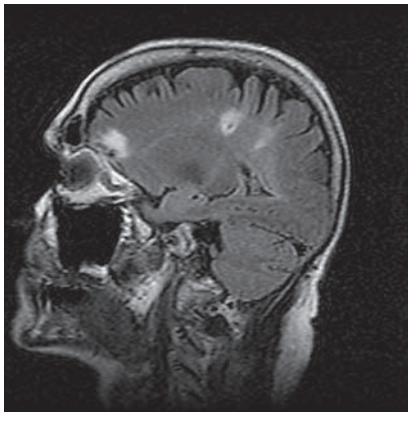
While epilepsy, or recurrent seizures, usually presents with obvious seizure manifestations, seizure without convulsions are possible.[13] In addition to motor, sensory and cognitive symptoms, seizure may be associated with nausea, headache and both positive and negative visual symptoms; however, it is uncommon for seizure to present with visual symptoms alone.[13,22] Subtle seizures in epilepsy may present with oculomotor signs such as nystagmus, abnormal repetitive blinking or eyelid flutter and tonic alignment deviations.[13]

Visual symptoms associated with seizure are quite diverse; they may appear as flashes, patterns or colors in the vision. Patterns can change and may look similar to a fortification pattern. Complex visual hallucinations, including perception of animals or people, may occur, as can image enlargement (macropsia) or reduction (micropsia), to name a few.

The visual phenomena may be stationary, traveling, localized or encompassing the entire visual field. Negative visual symptoms such as scotomas, ranging from focal to hemifield to complete visual loss, may also occur, though negative symptoms are less frequent than positive visual symptoms.[13,22]

Focal occipital seizure most frequently causes these visual phenomena, particularly the positive symptoms. Visual symptoms with seizure tend to be brief, lasting only a





Photos: Michael Trottini, OD, and Michael DeGiodice, OD

This patient presented emergently with a complaint of three isolated instances of "blue-colored shadows" that transiently and incompletely blocked the vision of the right eye for five minutes at a time. At left, her MRA revealed severe stenosis of the right internal carotid artery (ICA), and she was diagnosed with amaurosis fugax and right hemispheric subacute CVA secondary to severe right ICA stenosis. At right, imaging also showed two restricted diffusion foci located within the right posterior parietal-occipital junction, consistent with a subacute infarct.

few seconds, and may recur throughout the day.[13] If seizure is suspected, electroencephalogram (EEG) may help detect an epileptic wave of activity, though it may be difficult to detect in cases where only a small area of cortex is involved.[6,22]

Other visual hallucinations. Visual hallucinations may occur as a result of psychiatric disorders; alcohol intoxication or withdrawal; and LSD, marijuana, mescaline, digoxin or other drug use.[12,23] In these cases, the hallucination may be quite complex and may have accompanying auditory or other sensory hallucinations.[12]

Charles Bonnet syndrome, also known as visual release phenomenon, may also produce simple or complex visual hallucinations. This condition is seen in patients who have acquired vision loss for any number of reasons, whereby the visual cortex produces the perception of these hallucinations, thought to be due to chronic lack of sensory input (deafferentation).[24] Visual hallucinations in Charles Bonnet syndrome are not accompanied by any other sensory hallucinations.[23]

Positive visual phenomena, often a flickering sensation, may also occur

Case Report

A 70-year-old white male presented to the clinic with complaints of rainbows and lights in his vision. It had started about one week prior, and he described rainbows and shadows moving across the walls intermittently; he reported that he could see the rainbows and lights with either eye covered; he also reported that he saw some formed images, which he perceived as animals, but he recognized that other people could not see what he was seeing. He hadn't noticed any peripheral vision deficits.

When questioned, he said he had a headache a couple days prior to the onset of the visual symptoms, and his ex-wife had recently asked if he had developed some speech problems, but he himself hadn't noticed any changes. He denied tingling, weakness or numbness on either side of his face or body.

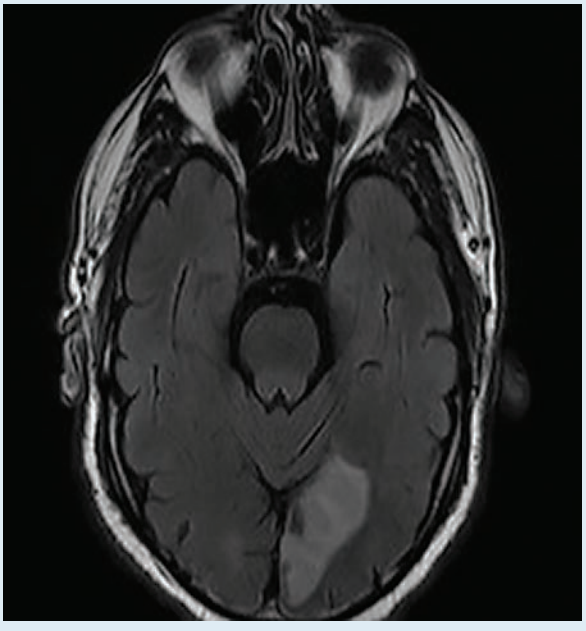
During the exam, it became quite apparent that the patient was confused and forgetful, and he exhibited some labile emotional responses (such as spontaneously starting to cry when asked questions). The patient's ocular health exam was largely unremarkable.

Given that the patient was experiencing a visual phenomenon with both positive and negative features and visual hallucinations, along with subacute confusion, he was escorted to our hospital's emergency department and was worked up for stroke.

He was diagnosed with a left occipital lobe (left posterior cerebral artery territory) subacute infarct with restricted diffusion extending into the left temporo-occipital region, and ultimately was admitted (*Figure 1*). Days after admission, the patient began to notice visual loss in the bottom right portion of his vision, and the neurologist noted that the patient had developed a right homonymous inferior quadrantanopia. Neurology initially thought his positive visual phenomena represented either simple focal seizures or were a result of the infarct itself.

An EEG indicated left hemispheric slowing and moderate encephalopathy but no epileptiform discharges or seizures. His visual hallucinations and positive visual phenomena persisted even beyond discharge; they varied from seconds to 30 minutes and presented from every hour to five to six times per day and predominantly presented in the inferior right quadrant of his vision, where he'd developed the visual field defect; at subsequent follow up, neurology felt his visual hallucinations were most consistent with visual release phenomenon. As evidenced by this patient, some cases of positive visual phenomenon can be quite complex.

This patient's positive visual phenomenon was the first stroke symptom, and, as his eye care provider, I was well-positioned to take a thorough history and ensure he was appropriately referred.



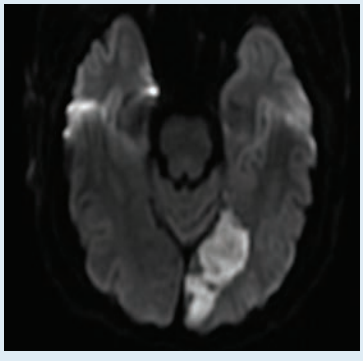


Fig. 1. These axial T2/FLAIR, left, and DWI, below, MRI images show hyperintensity in the left occipital lobe extending to the left temporo-occipital region, consistent with the patient's left posterior cerebral artery territory acute/subacute infarct.

due to systemic hypo- or hyperglycemia, or orthostatic hypotension.[25] Researchers have reported formed and unformed visual hallucinations, particularly in hyperglycemia, which may precede or accompany other systemic symptoms of hypeglycemia such as change in mentation.[26] These visual phenomena should subside with the normalization of systemic glucose or blood pressure.

Differentiating TIA, MAWH and Seizure

Visual symptoms are quite similar for seizure, MAWH, TIA and CVA. Migraines are frequently associated with epilepsy, as they share similar clinical features and pathophysiologic components; migraine and epilepsy may be concomitant, and the incidence of migraine in patients with epilepsy is about twice that of the general population.[13,27] Because positive visual phenomena from seizure are brief and rarely stand-alone, any additional seizure-like symptoms would warrant an evaluation by neurology.

No specific features uniformly differentiate TIA from migrainous visual phenomena, and neurological work up is generally normal for both.[7] Differentiating the two, however, is crucial, since TIA carries a 10% to 15% risk of subsequent stroke within three months, with half of those occurring within two days.[7,17] The long-term risk of stroke and major cardiac events such as myocardial infarction also increases; thus, misdiagnosing a TIA as a migrainous aura could have serious—potentially life threatening—implications.[7,17]

While no universal differentiators exist, some frequent differences between MAWH and TIA can help (*Table 1*). First, history is important; often, patients with MAWH have had a history of migraine earlier in life. Patients with TIA usually have vasculopathic risk factors for cerebrovascular disease such as diabetes and hypertension.

In addition, MAWH presents with bright, glistening, dynamic visual aura that gradually progresses, while TIA generally shows a largely negative visual phenomenon with a flat, static, non-progressive presentation that is maximum at onset. On neuroimaging, MAWH often has normal results; TIA must not show infarction, but often shows evidence of cerebrovascular ischemia, such as chronic small-vessel changes, and additional vascular testing would likely show atherosclerosis.[6]

In cases of positive visual phenomenon or aura that are inaugural in patients older than 40, if visual symptoms are purely negative or if the duration of aura is atypical for MAWH, the episode must be treated as TIA until proven otherwise, and clinicians must promptly initiate a full TIA evaluation.[16]

Positive visual phenomena may occur for a number of reasons not easily detectable on a comprehensive eye exam. Clinicians often need to order ancillary studies and consult with other disciplines to arrive at the appropriate diagnosis, or to rule out pertinent differentials before attributing a more benign diagnosis of exclusion to a patient's symptoms. Understanding the many potential underlying etiologies and other typical features of these conditions can help guide clinicians to the appropriate diagnosis and subsequent management. ■

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The Evolution of Migraine Headache/Aura and CBS Hallucination

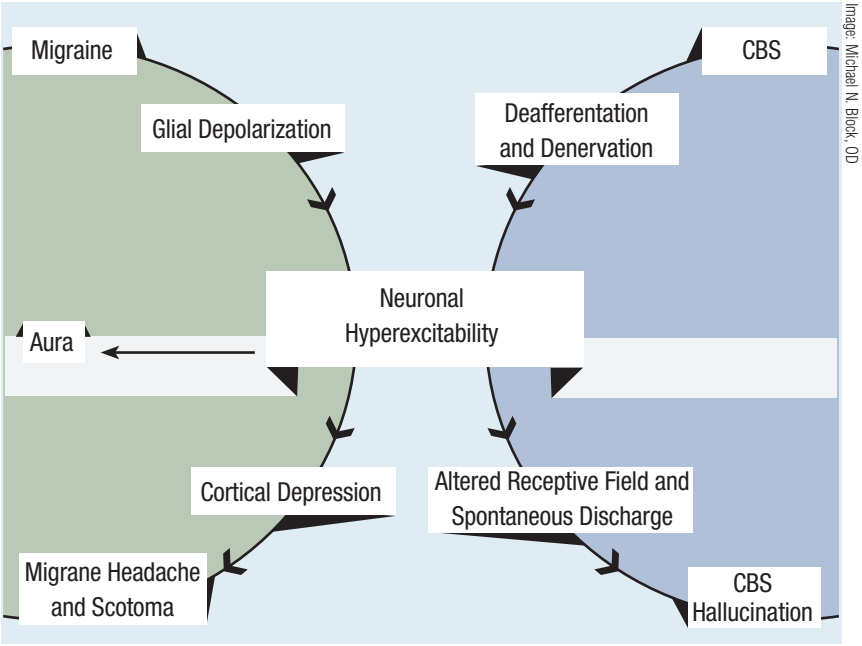

Image: Michael N. Block, OD

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1. Where is the source of entopic phenomena?
a. Inside the eye.
b. The orbit.
c. The chiasm.
d. The occipital cortex.

2. Which of the following is the most likely source of bilateral flashes in the vision?
a. Inside the eye.
b. The optic nerves.
c. The orbits.
d. The chiasm.

3. Which of the following is true of retinal arterial vasospasms?
a. They are a common cause of positive visual phenomena.
b. They usually cause permanent focal retinal arterial flow obstruction.
c. They are uncommon and are a diagnosis of exclusion.
d. They produce positive more often than negative visual symptoms.

4. Most cases of bilateral positive visual phenomena are due to:
a. Migraine aura.
b. Bilateral retinal detachments.
c. Seizures.
d. Strokes.

5. Migraine aura generally lasts how long?
a. Less than five minutes.
b. Five to 60 minutes.
c. 60 to 90 minutes.
d. More than 90 minutes.

6. Most migraine aura symptoms are:
a. Auditory.
b. Visual.
c. Speech related.
d. Motor (hemiplegic migraine).

7. Which of the following episodes similar to migraine aura without headache (MAWH) should be evaluated as if it were a transient ischemic attack (TIA)?
a. The first episode of MAWH.
b. Aura lasting less than five minutes.
c. Aura lasting longer than 60 minutes.
d. All of the above.

8. Which symptom is not typically consistent with TIA?
a. Sudden confusion.
b. Sudden numbness, tingling or weakness on either side of the face or body.
c. Left arm or chest pain or tightness.
d. Slurring of speech.

9. What neuroimaging, when immediately available and not contraindicated, is usually preferred in acute TIA or CVA?
a. Brain x-ray.
b. Brain MRI.
c. Brain CT.
d. Carotid Doppler ultrasound.

10. Which of the following is not typically associated with seizures?
a. Head trauma.
b. Intracranial lesions.
c. Intracranial ischemia or infarction.
d. Intraocular ischemia or infarction.

11. What oculomotor signs may be associated with seizure?
a. Nystagmus.
b. Abnormal repetitive blinking.
c. Eyelid flutter.
d. All of the above.

12. What focal seizures most frequently cause visual phenomena?
a. Parietal seizures.
b. Occipital seizures.
c. Temporal seizures.
d. Frontal seizures.

13. Which is true of visual hallucinations associated with Charles Bonnet syndrome?
a. They are accompanied by other sensory hallucinations.
b. They are due to sensory overstimulation of the visual cortex.
c. They may be simple or complex hallucinations.
d. They happen in people with normal vision.

14. Which of these systemic issues is not typically associated with positive visual phenomena?
a. Hyperglycemia.
b. Orthostatic hypertension.
c. Hypoglycemia.
d. Orthostatic hypotension.

15. After a TIA, what is the approximate risk of subsequent stroke within three months?
a. Less than 5%.
b. 10% to 15%.
c. 30% to 40%.

OSC QUIZ

d. More than 50%.

16. Of those who have a stroke within three months after a TIA, nearly half of those occur within what time frame?
a. Two days.
b. One week.
c. Two weeks.
d. Four weeks.

17. Which presentation of visual phenomena is most common with TIA?
a. Predominantly positive aura that is dynamic and progresses.
b. Predominantly positive aura that is flat and static.
c. Predominantly negative aura that is dynamic and progresses.
d. Predominantly negative aura that is flat and static.

18. Which presentation of visual phenomena is most common with MAWH?
a. Predominantly positive aura that is dynamic and progresses.
b. Predominantly positive aura that is flat and static.
c. Predominantly negative aura that is dynamic and progresses.
d. Predominantly negative aura that is flat and static.

19. What neuroimaging results are expected with MAWH?
a. Area of hemorrhagic stroke.
b. Area of ischemic stroke.
c. Occipital mass lesion.
d. Normal neuroimaging with no acute infarct.

20. What neuroimaging results are expected with TIA?
a. Area of hemorrhagic stroke
b. Area of ischemic stroke
c. Occipital mass lesion
d. Normal neuroimaging with no acute infarct.

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Post-activity evaluation questions:

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

21. Improve my clinical understanding of positive visual phenomena. ① ② ③ ④ ⑤
22. Become familiar with the ocular sources of positive visual phenomena. ① ② ③ ④ ⑤
23. Increase my understanding of non-ocular causes of positive visual phenomena. ① ② ③ ④ ⑤
24. Better identify the clinical features of migraine aura, transient ischemic attack and seizures. ① ② ③ ④ ⑤
25. Increase my clinical ability to differentiate the various source of positive visual phenomena. ① ② ③ ④ ⑤
26. Improve my ability to order the proper testing to confirm the cause of positive visual phenomena. ① ② ③ ④ ⑤

Rate the quality of the material provided:
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27. The content was evidence-based. ① ② ③ ④ ⑤
28. The content was balanced and free of bias. ① ② ③ ④ ⑤
29. The presentation was clear and effective. ① ② ③ ④ ⑤
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Heroes and Shields

Because VKC occurs mostly in children, swift, aggressive treatment is crucial.

Edited by Joseph P. Shovlin, OD

Q I have an 11-year-old patient with refractory severe vernal keratoconjunctivitis (VKC) and significant corneal staining, mostly in the left eye. I tried the typical topical agents such as low-dose steroids and mast-cell stabilizer/antihistamine drops. There is no shield ulcer yet, but I'm concerned it might happen. Are there any heroic options for this case?

A "VKC is a chronic issue, typically lasting several years with seasonal exacerbation," says Aaron Bronner, OD, of Pacific Cataract and Laser Institute. "That means even the most effective treatment regimen possible won't truly eradicate it, though it will burn out eventually." Also, it most typically occurs in children and adolescents, "which raises the stakes for both permanent sequelae of the disease, such a corneal scarring, and treatment, such as steroid-induced cataract development or increased intraocular pressure."

At its root, the condition is an inflammatory and allergic process, so reducing the inflammatory response is important. However, concerns about inconveniencing the patient or risk of treatment sequelae can get in the way of this step.

"In this case, the clinician treating the patient has raised concerns with potential for a shield ulcer, a problem that can cause permanent reduction in vision, should it develop," says Dr. Bronner. "This risk should trump any concerns over patient inconvenience or treatment sequelae risk. There is potential for the VKC to present a direct threat to vision, and that threat needs to be eliminated."

What Next?

Since a weaker steroid has already failed in this case, Dr. Bronner recommends a high-dose, high-potency corticosteroid such as Durezol (difluprednate, Novartis). Aggressive dosing is imperative to eliminate the inflammation. "Though there is a greater risk of steroid-related side effects with difluprednate compared with weaker steroids (especially in the juvenile population), its dosing duration should be short," says Dr. Bronner, "just long enough to control inflammation acutely before transitioning to the longer-term therapy with weaker steroids and antihistamine/mast-cell stabilizers. If a shield ulcer has already formed, the acute steroid therapy should be paired with an antibiotic."

Next up is what Dr. Bronner calls the long-term goal: keeping exacerbations as infrequent and as mild as possible. To do this, ODs should rapidly taper the steroid and move to a combination of the lowest dose and weakest steroid that maintains control. Mast-cell stabilizers/antihistamines should also be added to this treatment. "While short dosing of steroids is safe and effective, we know that the risk of cataracts and ocular hypertension rises with increased duration and frequency of steroid use," says Dr. Bronner. "Ideally, these patients will be tapered off of steroids for all periods other than acute flare-ups."

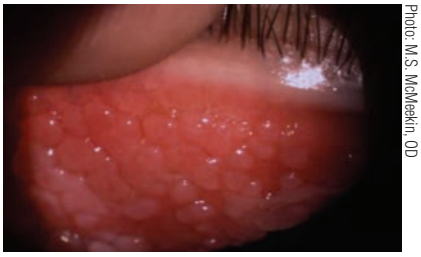

Photo: M.S. McMeekin, OD

VKC requires careful long-term therapy.

If the patient experiences a flare-up each time the steroid is reduced or eliminated, consider steroid-sparing therapies. "Compounded topical cyclcosporin A or tacrolimus have been shown to be effective at diminishing both signs and symptoms of VKC. However, keep in mind that stringent regulations have made it more difficult to find pharmacies to compound ophthalmic agents," says Dr. Bronner, "and there are also expected burdens with cost and insurance coverage."

Additionally, Dr. Bronner notes that "Restasis (cyclosporine 0.05%, Allergan) is generally too weak to be effective for cases of VKC."

Xiidra (lifitegrast, Shire) could be considered as an off-label, adjunctive treatment because "intercellular adhesion molecule-1 has also been shown to be upregulated in VKC," Dr. Bronner says.

"Though there are no clinical reports of Xiidra for maintenance therapy of VKC, it would likely be a safe approach and one with some scientific rationale; barring success with other, more standard therapy, I wouldn't hesitate to try it after counseling the patient appropriately." ■

Streaks of Concern

Although uncommon, angioid streaks often have a systemic cause and warrant prompt attention. **By Carlo J. Pelino, OD, and Joseph J. Pizzimenti, OD**

A 67-year-old Hispanic female presented with complaints of long-standing bilateral central visual field loss. She reported being diagnosed with age-related macular degeneration (AMD) nine years prior and receiving laser retinal treatment in each eye. Her health history was positive for Paget's disease and Type 2 diabetes.

Best-corrected visual acuities were 20/200 OD and 20/400 OS, both using eccentric viewing. Given her health history, we were unsurprised that dilated funduscopy revealed bilateral angioid streaks, moderate nonproliferative diabetic retinopathy and laser treatment scars in each eye. No drusen or other signs of AMD were evident (*Figure 1*).

This clinical picture led us to believe our patient did not have AMD; instead, she most likely developed choroidal neovascularization (CNV) associated with the contamination of Bruch's membrane that occurs with angioid streaks. She was referred to a low vision rehabilitation clinic, where she achieved success using various optical and non-optical devices.

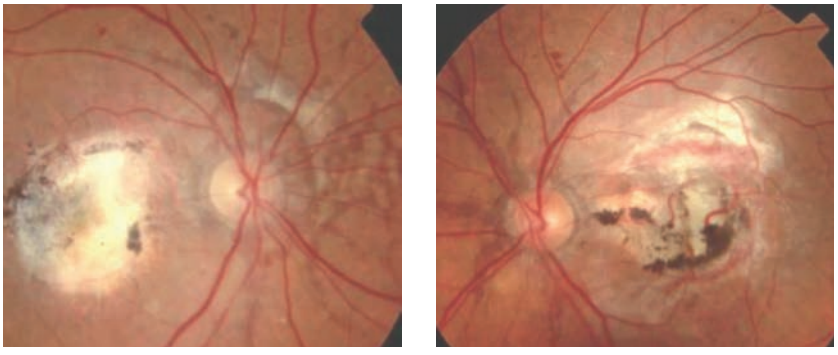

Fig. 1. This patient has angioid streaks that radiate from the optic disc, in addition to macular laser scarring and blot hemes.

A Streaky Past

This patient provides a classic example of angioid streaks—structural defects linked to several systemic conditions, the frequency of which increases with age. They occur at the level of Bruch's membrane, lying beneath normal retinal blood vessels, and typically present as bilateral deep red or grayish lines with irregularly serrated edges.[1]

When you see angioid streaks as a clinical sign, it's time to take a closer look at the patient's detailed history and review of systems, and conduct a thorough ophthalmic and, in most cases, systemic workup to determine the underlying cause.

Clinical Picture

Angioid streaks intercommunicate in a ring-like pattern around the optic disc in approximately 30% of cases and radiate outward from the disc in 70% of cases.[1,2] The streaks come to an abrupt end and seldom extend past the equator. Additional posterior segment findings in eyes with angioid streaks may include a peau d'orange or leopard-skin spotting that consists of speckled, yellowish mottling of the posterior pole, most apparent in the temporal aspect of the macula.

Peripapillary chorioretinal atrophy, focal peripheral chorioretinal scars, optic nerve head drusen and reticular pigment dystrophy of the macula may also be found in association with angioid streaks. In the event of blunt trauma, eyes with angioid streaks may be more likely to suffer vision loss due to the existing break in Bruch's membrane.[1,2]

Patients with angioid streaks are strongly advised to wear polycarbonate eyeglasses to protect against traumatic retinal damage. Because eyes with angioid streaks will

Table 1. Common Systemic Conditions Associated with Angioid Streaks

- Hemochromatosis
- Acromegaly
- Diabetes
- Sickle-cell hemoglobinopathies
- Pseudoxanthoma elasticum
- Acquired hemolytic anemia
- Myopia
- Neurofibromatosis
- Paget's disease
- Ehlers–Danlos syndrome

always be at risk for CNV due to the damage to Bruch's membrane, they should have eye exams at regular intervals.

CNV in the peripapillary and macular regions can occur in a small percentage of patients with angioid streaks, leading to severe vision loss.[3] The visual prognosis, if untreated, is poor, and most traditional treatment modalities have failed to limit the devastating impact on central vision. However, research shows novel treatment with anti-VEGF agents may yield favorable results.[1,4,5] The researchers also found early treatment and extended follow up were critical to therapeutic success.[5] To help detect CNV early, clinicians should perform optical coherence tomography in addition to dilated funduscopy at each follow up visit.[1]

Systemic Involvement

While angioid streaks should raise suspicion of a serious underlying systemic condition, the patient's whole clinical picture will help you uncover the exact etiology (*Table 1*).

Pseudoxanthoma elasticum (PXE) is an inherited connective tissue disorder. It affects elastin fibrils in the skin's dermis layer, and appears as yellow papules known as "chicken skin." PXE may cause changes in arterial walls, the heart, gastrointestinal tract and Bruch's membrane, causing mineralization and deposition of phosphorus. Cardiovascular findings in PXE may include hypertension due to atherosclerosis, coronary artery disease, peripheral vascular disease and mitral incompetence. Neurological findings may include cerebrovascular accident, intracranial aneurysms and cerebral ischemia.[5]

Of patients with PXE, 85% develop ocular involvement, referred to as Grönblad–Strandberg syndrome.[6] In addition to angioid streaks, the literature reports other fundus lesions, including optic disc drusen, macular pattern dystrophy, crystalline bodies and midperipheral "comet-tail" atrophic spots.[6]

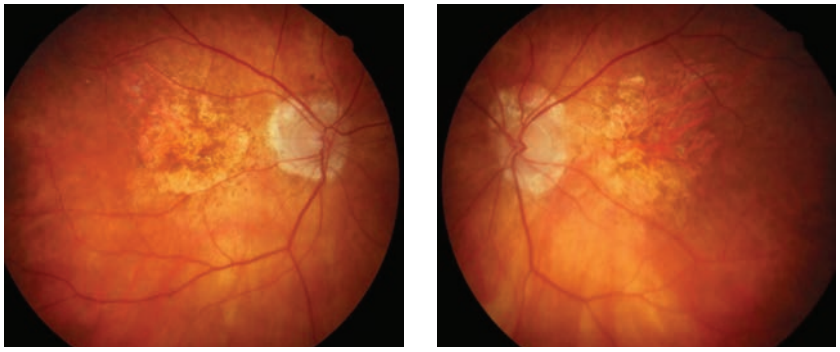

Fig. 2. Advanced atrophic AMD may masquerade as angioid streaks.

Ehlers-Danlos syndrome is a disease of collagen resulting from a deficiency of hydroxylysine. Patients may develop dermatologic, musculoskeletal, cardiovascular, gastrointestinal and respiratory signs and symptoms. Ocular complications include epicanthal folds, keratoconus, high myopia, retinal breaks and detachment, ectopia lentis, blue sclera and angioid streaks.[1]

Paget's disease, our patient's diagnosis, is a chronic, progressive condition whose key clinical feature is bone deformity. It may become evident as an enlargement of the skull, deafness and malformation of long bones. Angioid streaks and optic atrophy are the main ocular manifestations.[7]

Hemoglobinopathies occasionally associated with angioid streaks include homozygous sickle cell disease, sickle cell trait, sickle cell thalassemia, sickle cell hemoglobin, hemoglobin H, homozygous B-thalassemia major, intermedia and minor, and hereditary spherocytosis. The frequency of angioid streaks in the hemoglobinopathies increases with age, with a rate of occurrence of approximately 1.5% in younger patients and 22% in patients 55 and older.[1,8,9]

Other systemic conditions that may be associated with angioid streaks include acromegaly, dwarfism, diabetes mellitus, idiopathic thrombocytopenia purpura and acquired homolytic anemia. Researchers have also reported cases of angioid streaks in patients with lead poisoning.[1,9]

After an extensive workup with negative findings for common systemic associations, some

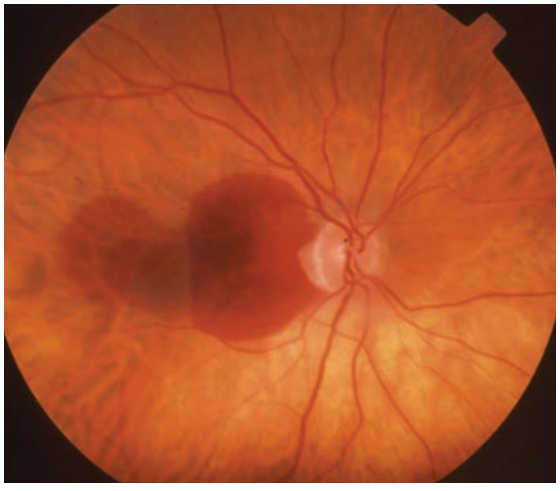

Fig. 3. CNV and subretinal hemorrhage in an eye with past trauma.

Paul Karpecki, OD, FAAO

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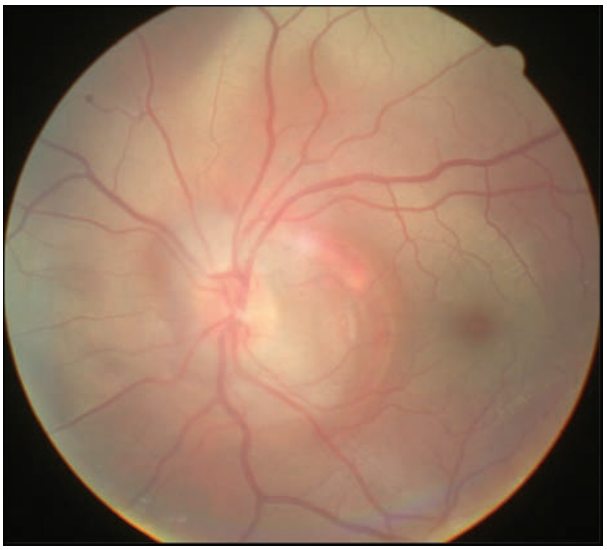

Fig. 4. Traumatic choroidal rupture may also injure Bruch's membrane, leading to CNV.

patients may be diagnosed with idiopathic angioid streaks.

Masqueraders

Clinicians should always be on the lookout for conditions that can mimic angioid streaks. Among the most common are exudative and advanced atrophic AMD, choroidal rupture, toxoplasmosis, choroidal sclerosis, myopic lacquer cracks, histoplasmosis, retinal vasculitis and papillitis and traumatic retinal hemorrhage with or without CNV (*Figures 2-4*).[1]

Angioid streaks, resulting from damage to the elastic lamina of Bruch's membrane, are often harbingers of systemic conditions and warrant immediate attention by eye care providers. Early diagnosis is vital to minimize functional vision loss due to any resulting CNV or trauma. ■

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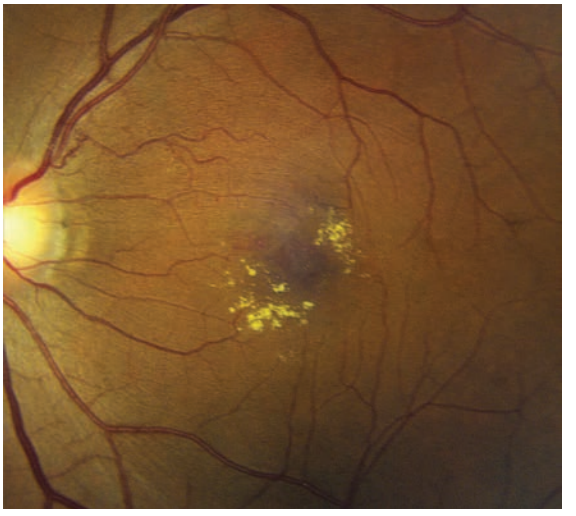
9. Paton D. Angioid streaks and sickle cell anemia. Arch Ophthalmol. 1959;62(5):852-8.

Leak Investigation

A recent cataract surgery patient showed some unusual findings in a postoperative exam, but is it related to the procedure? **By Mark T. Dunbar, OD**

A 72-year-old Hispanic female presented to our office for her postoperative eye exam. She had undergone an uncomplicated cataract surgery along with intraocular lens (IOL) implantation four weeks earlier in her left eye.

The right eye had prior cataract extraction approximately eight weeks earlier. She was extremely happy with her visual outcome and had stopped using her drops.



Posterior pole image of the left eye of our patient. How do you explain these finding in a patient who recently had cataract surgery?

Evaluation

On exam, her best-corrected visual acuity was 20/20 OD, 20/30 OS. Confrontation fields were full-to-careful finger counting in both eyes. The pupils were equally round and reactive to light. There was no afferent pupillary defect.

Anterior segment examination was significant for posterior chamber IOL implants that were well centered and clear visual axes.

Dilated fundus exam showed moderate-sized cups with good rim coloration and perfusion in both eyes. The right eye was completely normal. Upon exam, the left eye showed changes.

Optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A) images were also obtained and are available for review.

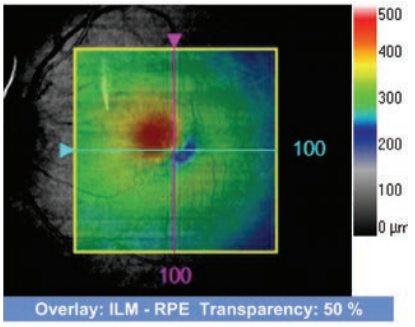
Take the Retina Quiz

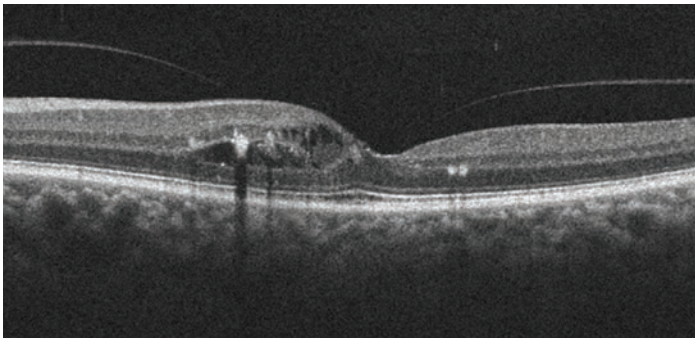
1. What do the yellow changes in the macula represent?
a. Drusen.
b. Lipofuscin.
c. Hard exudate.
d. Calcium.

2. How would you characterize the spectral-domain OCT?
a. Localized ischemia.
b. Intraretinal neovascularization.
c. Macular thickening with intraretinal fluid.
d. Macular thickening with subretinal fluid.

3. Based on the clinical appearance, what is the overall diagnosis?
a. Coats' disease.
b. Macular telangiectasis.
c. Branch retinal vein occlusion.
d. Irvine-Gass Cystoid macular edema.

4. How should this patient be managed?





SD-OCT images through the macula of the 72-year-old patient's left eye.

a. Focal laser treatment to the macula.
b. Intravitreal kenalog.
c. Intravitreal anti-VEGF injection.
d. Observation.

For answers, see page 82.

Discussion

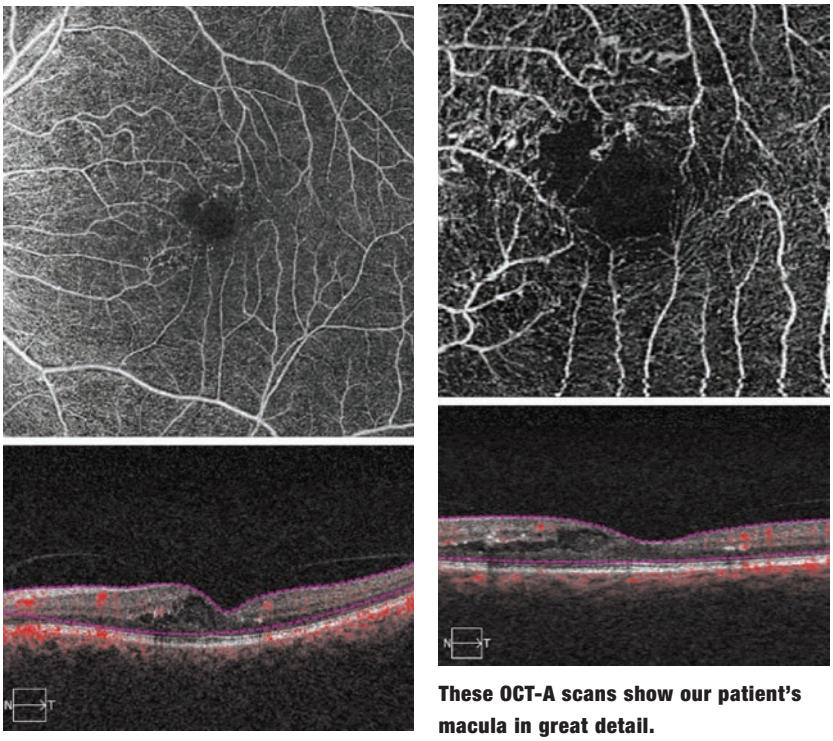
The yellow precipitates in the macula represent hard exudate. On clinical exam, it was evident that the macula was thickened and there was edema. The spectral domain optical coherence tomography (SD-OCT) confirmed retinal thickening as well as intraretinal fluid and mild cystoid macular edema. The 3D thickness map highlights this nicely, where the red area represents a localized area of retinal thickening.

Diagnosis Decisions

So, what is going on with our patient? Are these changes related to her cataract surgery? The OCT-A provides some valuable insight as to the cause. Microvascular changes are clearly visible on the OCT-A scan as well as some collateral vessel formation around the superior portion of the foveal avascular zone.

Based on these findings, we can surmise that our patient has a small branch retinal vein occlusion (BRVO). Another clue to this etiology is the presence of the anomalous vessel superior to the disc that can be seen in the color fundus photo. It looks like it may be a dilated collateral vessel. Perhaps this is the location where the occlusion occurred.

It's difficult to know for how long she has had the occlusion or where she is in the course of the disease. It was not present two months prior when she was being examined for her cataracts. The usual presentation of BRVO is a triangular or wedge-shaped area of hemorrhage that extends beyond the site of where the artery crosses the vein. Our patient doesn't have that. This could be because it is almost resolved and we are seeing her in the resolution phase, or because it was a very mild retinal vein occlusion to begin with.



These OCT-A scans show our patient's macula in great detail.

As the hemorrhage from the occlusion resolves, there are still some leaking and incompetent retinal vessels that are releasing exudate that extends into the macula, resulting in macular edema. One thing is for certain: it's not related to her cataract surgery.

There is a strong association between hypertension and the development of retinal vein occlusion. Our patient does, in fact, have hypertension, but it is well controlled with Norvasc (amlodipine, Pfizer) and hydrochlorothyiazide. So, is the small BRVO a result of her high blood pressure? It is impossible to know the true effect of the patient's hypertensive status on her vision because approximately half of all patients with RVOs have hypertension. Regardless, it is important that the hypertension be controlled.

Management

Anti-VEGF therapy has emerged as the standard of care in treating macular edema associated with retinal vein occlusions. Lucentis (ranibizumab, Genentech), Avastin (bevacizumab, Genentech) and Eylea (aflibercept, Regeneron) are all potential treatment options for our patient.

Even though our patient has mild macular edema and this condition could resolve on its own, we referred her to the retinal specialist for consideration of treatment. ■

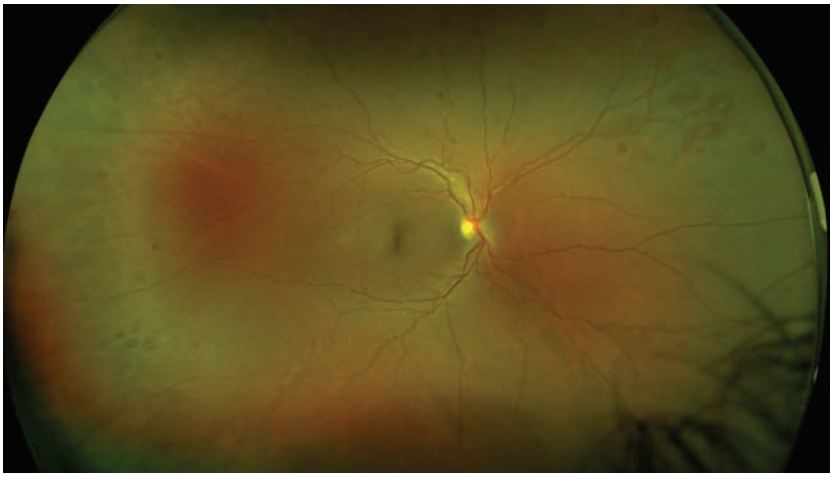
1. Interim Guidelines for Management of Retinal Vein Occlusion; Royal College of Ophthalmologists (December 2010). www.rcophth.ac.uk/wp-content/uploads/2015/07/Retinal-Vein-Occlusion-RVO-Guidelines-July-2015.pdf. Accessed: December 15, 2017.


Spot the Dot

When an OD notes this unusual presentation, it's time to spring into action.

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

A 51-year-old black woman presented for ocular examination complaining of blurry vision in both eyes. Her ocular history was unremarkable, but her systemic history was complex. In addition to hypertension, she had cardiovascular disease, thyroid disease, asthma, herpes zoster and multiple strokes, the most recent of which was one year ago. Currently under the care of an internist and a cardiologist, her medications included metoprolol, furosemide, spironolactone, digoxin, levothyroxine, baby aspirin, Xarelto (rivaroxaban, Janssen) and Protonix (pantozaprole, Pfizer).



Our patient's right fundus demonstrates scattered midperipheral, white-centered retinal hemorrhages. Similar findings also appeared in the left fundus.

Evaluation

Upon examination, best-corrected visual acuity was 20/20 OD and 20/25+ OS. Motilities and visual fields by confrontation were normal in both eyes, and pupils were reactive without afferent defect. Intraocular pressures (IOP) were 20mm Hg OD, 23mm Hg OS. Examination of the anterior segment revealed mild lenticular changes, but was otherwise unremarkable. Fundus evaluation disclosed a pink, healthy optic disc and an intact fovea in each eye. The retinal vasculature was mildly dilated and tortuous in both eyes, with minimal crossing changes. Of note, there were multiple, deep, round retinal hemorrhages, many with distinctively white centers, primarily located in the midperiphery of both eyes. There was no evidence of macular edema, retinal exudate, cotton-wool spots or neovascular changes in either eye.

White-centered retinal hemorrhages— commonly known as "Roth spots"—can be an alarming finding for any eye care practitioner. These lesions are believed to represent a rupture of retinal capillaries, with extrusion of blood and subsequent platelet adhesion to the damaged endothelium.[1,2] The release of platelets initiates a coagulation cascade, which leads to the formation of a platelet-fibrin thrombus; this accounts for the white center of each hemorrhagic lesion.[1,2]

For years, Roth spots were believed to be pathognomonic for subacute bacterial endocarditis, a potentially life-threatening infection of the cardiac endothelium.[1-6] Today, however, we recognize that these lesions can be encountered in numerous other conditions, including hypertensive and diabetic retinopathy, as well as connective tissue disorders such as systemic lupus, ankylosing spondylitis and Behçet's disease.[1,2,4,7,8] Additionally, other infectious diseases may present with this retinal finding, including toxoplasmosis, leishmaniasis and human immunodeficiency virus (HIV).[9-11] Numerous blood dyscrasias have also been associated with Roth spots, and this finding can portend such insidious conditions as anemia, thrombocytopenia and even several types of leukemia.[2,5,12-16] Rarely, Roth spots have been noted in association with anoxia and carbon monoxide poisoning, severe head trauma (especially in children and infants) and intracranial hemorrhage.[1,12,16-18] The central stimulating factor seems to be increased capillary fragility, intravascular coagulopathy or both.[4]

Testing Protocol

When funduscopic exam reveals Roth spots, particularly in cases where the medical history is unknown or reportedly unremarkable, a systemic evaluation for disease is crucial. Initial testing should include an assessment for hypertension, a fasting plasma glucose test, serum lipid profile, complete blood count with differential and an erythrocyte sedimentation rate. These tests will help identify the vast majority of conditions mentioned, including diabetes, hypertension and hyperlipidemia, blood dyscrasias and potential collagen-vascular disorders. Additional tests can include blood cultures, cardiac evaluation and specific serology for infectious disorders or autoimmune disease.

If the patient is not in acute distress, and if they have an established primary care provider (PCP), we coordinate care with that physician rather than ordering testing directly. In most cases, the PCP has detailed knowledge of the patient's condition and medications that may provide additional insight, thereby reducing the number of diagnostic tests required. Also, the PCP will ultimately be the one to initiate treatment for any underlying disease, and having the laboratory results sent directly to that individual facilitates more efficient care of the patient.

Comanagement

In our case, we elected to communicate with the PCP and inform him of the noted changes. We reviewed the potential etiologies associated with white-centered hemorrhages and suggested the diagnostic evaluation. We also asked about rivaroxaban—which has been associated with retinal hemorrhages in several case reports—and whether that or any of her other medications might be potentiating the anticoagulation effect.[19] Neither we nor the PCP were aware of any reports of Roth spots associated with the use of rivaroxaban or any other anticoagulants. Moreover, the only potential drug interaction in this case was between rivaroxaban and aspirin. While numerous drugs can potentiate warfarin, the newer generation anticoagulants are specific inhibitors of clotting factors and are not linked to vitamin K use.[19] For this reason, the list of medications and other supplements that should be avoided is far smaller for rivaroxaban than for warfarin.

At press time, we were still awaiting results of this patient's diagnostic laboratory evaluation. ■

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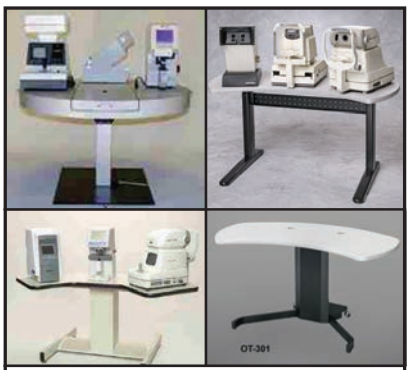

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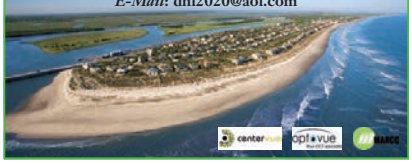

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Meetings + Conferences

February 2018

■ **9-11.** *57th Annual Heart of America Eye Care Congress*. Sheraton Kansas City Hotel at Crown Center, Kansas City, MO. Hosted by: Heart of America Eye Care Congress. Key faculty: Marc Bloomenstein, Alan Glazier, Blair Lonsberry, Justin Schweitzer. CE hours: 63 total, 17 per OD. For more information, email Ron Fiegel at registration@hoaecc.org or go to hoaecc.org.

■ **9-11.** *34th Annual Palm Beach Winter Seminar*. Hilton West Palm Beach, West Palm Beach, FL. Hosted by: Palm Beach County Optometric Association. Key faculty: Bruce Onofrey, Greg Caldwell. CE hours: 20. For more information, email Tamara Maule at pbwinterseminar@gmail.com, call (561) 477-3524 or go to www.pbcoa.org.

■ **10-17.** *Tropical CE— Cap Cana 2018*. Secrets Cap Cana Resort & Spa, Punta Cana, Dominican Republic. Hosted by: Tropical CE. Key faculty: Ben Gaddie, Walter Whitley. CE hours: 20. For more information, email Stuart Autry at sautry@tropicalce.com, call (281) 808-5763 or go to www.tropicalce.com.

■ **16-18.** *Optometric Education Consultants Mid-Winter Educational Getaway*. JW Marriott Scottsdale Camelback Inn Resort & Spa, Scottsdale, AZ. Hosted by: Optometric Education Consultants. Key faculty: Greg Caldwell, Joseph Sowka, Joseph Pizzimenti, Andrew Gurwood, Marc Meyers. CE hours: 15. For more information, email Vanessa McDonald at optoec@gmail.com, call (954) 262-4224 or go to www.optometricedu.com.

■ **16-18.** *Final Eyes CE 2018*. DuPont Auditorium, Baptist Medical Center, Jacksonville, FL. Hosted by: Florida Eye Specialists. Key faculty: Edward Bennett, Rajesh Shetty, Richard Van De Velde, Harry S. Campbell, Carlo Pelino. CE hours: 18. For more information, email Susan Frick at finaleyesce@gmail.com, call (904) 200-1852 or go to finaleyesce.com.

■ **16-20.** *Winter Ophthalmic Conference*. Westin Snowmass Conference Center, Aspen, CO. Hosted by: *Review of Optometry*. Key faculty: Murray Fingeret, Leo Semes. CE hours: Up to 20. For more information, email Lois DiDomenico at reviewmeetings@jobson.com, call (866)730-9257 or go to www.skivision.com.

■ **28-March 4.** *SECO 2018*. Georgia World Congress Center, Atlanta. Hosted by: SECO International. Key faculty: Brad R. Grimsley, William J. Harbour, Donald R. Korb, Jay Haynie, Justin Bazan, Jenn Lim. CE hours: 178 total, 209 staff, 46 per OD. For more information, email Elizabeth Taylor DeMayo at etaylor@secostaff.com, call (770) 451-8206 or go to attendseco.com.

March 2018

■ **4-9.** *32nd Annual EyeSki Conference*. Shadow Ridge Conference Center, Park City, UT. Hosted by: EyeSki. Key faculty: Joseph Pizzimenti, Leonard Messner, Tom Arnold, Mile Brujic, James Fanelli. CE hours: 22. For more information, email Tim Kime at tandbkime@buckeye-express.com, call (419) 475-6226 or go to www.eyeskiutah.com.

■ **7-11.** *Ocular Therapeutics in Cancun*. Fiesta Americana Condesa All Inclusive Resort, Cancun, Mexico. Hosted by: Ocular Therapeutics CE. Key faculty: Anthony Litwak, Diana Shechtman, James Thimons. CE hours: 20. For more information, email Anthony Litwak at info@otce.net, call (443) 895-1682 or go to www.otce.net.

■ **15-18.** *International Vision Expo & Conference East*. Jacob Javits Center, New York City. Hosted by: Reed Exhibitions and The Vision Council. Key faculty: Ben Gaddie, Mark Dunbar, Kirk Smick, Jack Schaeffer, Dave Ziegler, Douglas Devries. CE hours: 275 total, 30 per OD. For more information, go to east.visionexpo.com.

April 2018

■ **6-8.** *New Technologies & Treatments in Eye Care*. Nashville Marriott at Vanderbilt, Nashville. Hosted by: *Review of Optometry*. Key faculty: Paul Karpecki. CE hours: Up to 19. For more information, email Kristina Furner at kfurner@jobson.com, call (610) 492-1009 or go to www.reviewofoptometry.com/nashville2018.

■ **19-21.** *MWCO Annual Congress*. Aria Resort & Casino, Las Vegas. Hosted by: Mountain West Council of Optometrists. Key faculty: Alison Bozung, John McGreal, Julie Rodman, Jessica Steen, Jim Thimons, Rob Wooldridge. CE hours: 56 total, 24 per OD. For more information, email Tracy Abel at mountainwestcouncil@gmail.com, call (888) 376-6926 or go to www.mwco.org.

■ **25-28.** *Innovations in Optometry*. Harbour Town Clubhouse Sea Pines Resort, Hilton Head Island, SC. Hosted by: Brittany Stiegemeier. Key faculty: John Schachet, Bill Potter, Jeff Genos, Leo Semes, Howard Purcell, Ryan McKinnis, Peter Shaw, Jason Jedlicka, Nathan Lighthizer. CE hours: 19. For more information, email Brittany Stiegemeier at brittany@innovationsinoptometry.com or call (937) 623-1690.

■ **26-29.** *New Technologies & Treatments in Eye Care San Diego/OCCRS Joint Symposium*. San Diego Marriott Del Mar, San Diego. Hosted by: *Review of Optometry* & OCCRS. Key faculty: Paul Karpecki, David Friess. CE hours: Up to 28. For more information, email Lois DiDomenico at reviewmeetings@jobson.com, call (866) 658-1772 or go to www.reviewofoptometry.com/sandiego2018.

To list your meeting, please send the details to:

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Ram On

By Andrew S. Gurwood, OD

History

A 76-year-old female presented emergently with a chief complaint of "a dark spot" in the visual field of her right eye of one day's duration. Her ocular history was remarkable for uncomplicated bilateral cataract extraction in 2010. She did not report any recent ocular or head injury. Her systemic history was significant for hypertension, hypercholesterolemia and Type 2 diabetes, for which she was medicated with losartan/HCTZ, atorvastatin and glipizide. She reported no allergies.

Diagnostic Data

Her entering corrected visual acuities measured 20/120 OD with no improvement on pinhole and 20/30- OS. Her extraocular muscle movements were full and without pain, there was no afferent pupillary defect and the vision could not be improved with refraction, but she was able to position the black spot using the facial Amsler grid. Color vision was unaffected. Biomicroscopy of the anterior segment found normal structures and open angles with Goldmann intraocular pressures measuring 13mm Hg OU. The dilated fundus findings are demonstrated in the photographs.

Your Diagnosis

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

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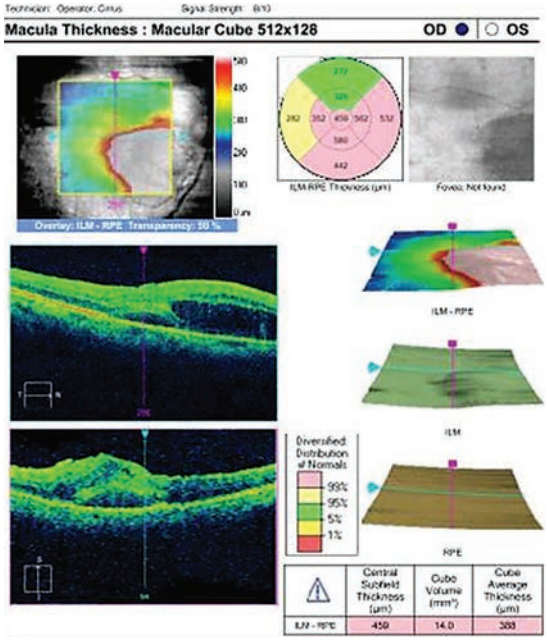
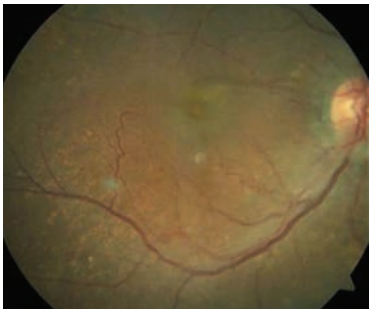
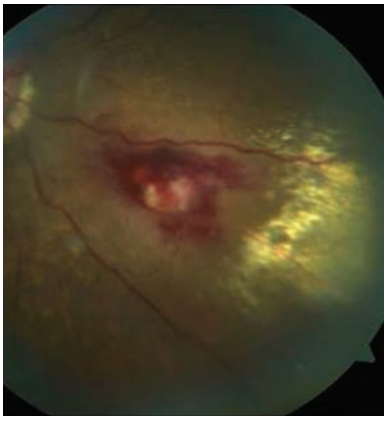
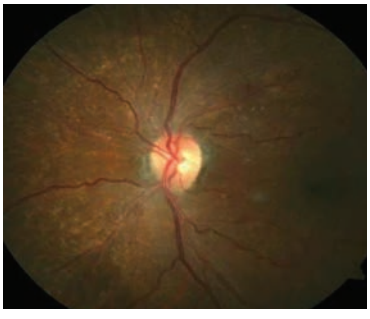


At left, OCT imaging of our 76-year-old patient who complained of a "dark spot" in her vision.

Below, the top two fundus images show the patient's right eye and the bottom fundus image shows the left eye. Can you identify the cause of the patient's visual disruption?







Retina Quiz Answers

(from page 74):

1) a; 2) c; 3) d; 4) d.

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