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REVIEW[®] of Ophthalmology

October 2020

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ISSUE FOCUS: CORNEA

CORNEAL CROSS-LINKING MOVES FORWARD

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cornea-saving procedure. P. 34*

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References: 1. Omeros survey data on file. 2. OMIDRIA [package insert], Seattle, WA: Omeros Corporation; 2017. 3. Al-Hashimi S, Donaldson K, Davidson R, et al; for ASCRS Refractive Cataract Surgery Subcommittee. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg.* 2018;44:1032-1041.

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Pediatric Ophthalmology Hit Hard by Pandemic

An article in press at the *Journal of the American Association for Pediatric Ophthalmology and Strabismus* published a survey of pediatric ophthalmologists that quantified the significant impact the pandemic has had on them and, by extension, their patients.

The AAPOS says that the effects of the pandemic on their practices “portend access-of-care issues for children with blinding, if not life-threatening, diseases. As pediatric specialists struggle to keep their practices viable, children in America may suffer medical outcomes not anticipated in first-world countries.”

On the survey, which was administered in April 2020, the loss of clinic revenue was 76 to 100 percent in fully 75 percent of all responding practices (304/405). Overall, 93 percent of practices (377/405) reported at least a 51-percent loss of clinical revenue. For 93 percent of respondents (378/405), surgery revenue decreased by at least 76 percent during the survey period.

This survey also found that nearly 90 percent of pediatric ophthalmologists were either furloughed or had their salaries reduced; 10 percent of those in private practice filed for unemployment. If practices close, or limit Medicaid patients’ access to services—which the numbers on the survey indicate is a possibility—this will have an impact on economically-disadvantaged families’ access to care, the authors say.

Pediatric ophthalmologist Janine Collinge, MD, who practices at Connecticut Children’s Specialty Group,

says the threat to patients is real. “The government programs that assisted practices based on medicare volumes left predominantly pediatric practices and childrens’ hospitals in the lurch for how they were going to find financial support to survive,” she says. “Pediatric ophthalmology is already an underserved subspecialty, so this field is not necessarily amenable to tolerating the stresses of COVID the way other fields may be.”

In addition to the economic impact, the survey also detailed how the infection risk—or just the fear of infection—has the potential to hinder patient care for kids who really need it. The authors explain that recent studies have shown that this coronavirus can spread readily through crying or screaming, two behaviors associated with pediatric patients. The article cites data from a personal communication with Maurice O’Gorman, PhD, Chief of Laboratory Medicine at Children’s Hospital Los Angeles. The article states, “testing of healthy, asymptomatic preoperative patients in the Southern California/Los Angeles area found that 1.9 percent of asymptomatic children were COVID-19 positive. This rate of positivity increased in tested children from local pediatric clinics, with degree of positivity noted with symptoms of 5.8 to 21.6 percent. Similar tests confirmed that nearly 10 percent of children in the Los Angeles area are COVID-19 antibody positive. Extrapolating from O’Gorman’s data, a daily pediatric ophthalmology clinic of 50 patients in Southern California

could be expected to have at least one presymptomatic child carrying COVID-19.”

Risk of Infection During Exams

Since every ophthalmologist wonders about the risk of infection during a routine clinic day, a group of ophthalmologists in Izmir, Turkey, performed an experiment that was published in the September issue of *JAMA Ophthalmology*.

In their report, the physicians say that, though person-to-person contact through airborne droplets is believed to be the main route of viral transmission, some have suggested that contaminated surfaces might also play a role. They cite a study of cruise-ship outbreaks of SARS-CoV-2 that found viral RNA on the surfaces in ships’ cabins up to 17 days after patients disembarked.¹ Another study reported viable SARS-CoV-2 in aerosols up to three hours post-aerosolization.² They note, however, that the latter study didn’t mimic ophthalmic exam room conditions, but instead used a nebulizer and a Goldberg drum that generates aerosols. “An important limitation of lab studies is the difficulty of evaluating individuals who are infected and asymptomatic in routine ex-

aminations,” the authors wrote. “Since we are examining patients who are asymptomatic during the pandemic, we wanted to know if we could detect COVID-19 viral material at the end of a day of examinations of patients who were asymptomatic and seen in an eye examination room.”

Before beginning the study, the researchers eliminated patients with symptoms, as well as patients and companions with a history of travel to affected areas (March 2020) or who had had contact with confirmed or suspected COVID-19 cases. In the exam room, they used a plastic shield on the slit lamp.

The room was cleaned and remained unused before the study. During the study, chin and forehead rests were wiped with isopropyl alcohol between patients. The same physician performed all exams, and one health-care worker visited the room.

The researchers divided the room into five zones (See Figure 1), set up as concentric circles, with the patient’s chair in the center (zone 1). Samples were taken at each 1 m of distance away from zone 1, eventually defining the five zones. According to the zone definition, the slit lamp shield, biomicroscope stage and phoropter were in zone 1; the tonometer was in zone 2; the desk was situated in zones 3 and 4; and the door handles were in zone 5.

The day of the experiment, 29 patients came to the hospital for an exam. Seven of them were directed for COVID-19 tests following triage and didn’t go to the exam room. Overall, 31 visitors entered the room, of whom 22 underwent exams. The mean exam time was 9 ±4 minutes (range: 5 to 13 minutes). One ophthalmologist collected

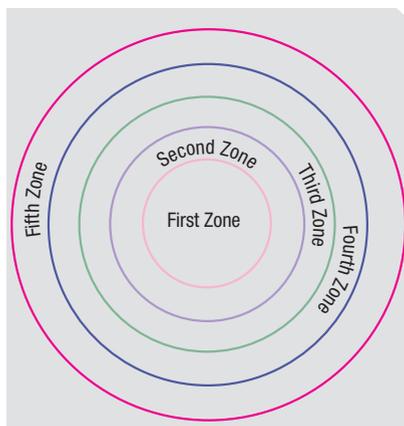


Figure 1. Researchers divided an exam room into zones (with the exam chair in the center), then took samples from each zone to look for coronavirus.

14 samples from the surfaces in the room—seven before the exams and seven after. All pre-exam samples were negative. Two post-exam samples that were collected from zone 1—from the slit lamp shield and phoropter—were found to be positive for SARS-CoV-2 viral material.

Though the study gives an idea of the potential risk from asymptomatic patients, the authors acknowledge its limitations: The RT-PCR testing that was used on the samples only confirms the presence of viral material, but not the viral load or infectivity of it. It was also a small sample size. The authors wrote, “it was not known whether patients, companions and the health-care worker developed symptoms... Further studies are needed to determine the clinical relevance of these findings.” **REVIEW**

1. Moriarty LF, Plucinski MM, Marston BJ, et al. Public health responses to COVID-19 outbreaks on cruise ships—worldwide, February–March 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:12:347–352.
 2. an Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med* 2020;382:16:1564–1567.

Correction

In the September issue, in the article “Techniques & Tools for Managing Dry Eye,” the table on page 39 lists the manufacturer of the product Cyclokot as “Noavali” instead of Novagali, and the product CyclIASol was misattributed to Novagali. CyclIASol is a Novaliq product. *Review* regrets the errors.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use LOTEMAX[®] SM safely and effectively. See full prescribing information for LOTEMAX[®] SM.

LOTEMAX[®] SM (loteprednol etabonate ophthalmic gel) 0.38%

For topical ophthalmic use

Initial U.S. Approval: 1998

INDICATIONS AND USAGE

LOTEMAX[®] SM is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops. Apply one drop of LOTEMAX[®] SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX[®] SM, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

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

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

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

Bacterial Infections: Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

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

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

Contact Lens Wear: Contact lenses should not be worn when the eyes are inflamed.

ADVERSE REACTIONS

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. Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

USE IN SPECIAL POPULATIONS

Pregnancy: Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate

produced malformations when administered orally to pregnant rabbits at doses 4.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 106 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 10.6 times the RHOD. Maternal toxicity was observed in rats at doses 1066 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 106 times the RHOD. 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 loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (4.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (17 times the RHOD). At 3 mg/kg (128 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (256 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (106 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (1066 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (10.6 times the clinical dose), reduced survival was observed in live-born offspring. Doses \geq 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses \geq 50 mg/kg (1066 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

Lactation: There are no data on the presence of loteprednol etabonate 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 LOTEMAX[®] SM and any potential adverse effects on the breastfed infant from LOTEMAX[®] SM.

Pediatric Use: Safety and effectiveness of LOTEMAX[®] SM in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in the chromosomal aberration test in human lymphocytes, or *in vivo* in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (106 times the RHOD).

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Clinical significance of these preclinical data has not been established.

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(loteprednol etabonate ophthalmic gel) 0.38%

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*PROVEN STRENGTH

- 30% of LOTEMAX® SM patients had complete ACC resolution vs vehicle (15%) at Day 8 (N=371, P<0.0001)^{1,2†}
- 74% of LOTEMAX® SM patients were completely pain-free vs vehicle (49%) at Day 8 (N=371, P<0.0001)^{1,2‡}

†Pooled analysis of Phase 3 clinical studies. **Study 1:** 29% LOTEMAX® SM (N=171) vs 9% vehicle (N=172). **Study 2:** 31% LOTEMAX® SM (N=200) vs 20% vehicle (N=199); P<0.05 for all.

‡Pooled analysis of Phase 3 clinical studies. **Study 1:** 73% LOTEMAX® SM (N=171) vs 48% vehicle (N=172). **Study 2:** 76% LOTEMAX® SM (N=200) vs 50% vehicle (N=199); P<0.05 for all.

Indication

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information

- LOTEMAX® SM, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If LOTEMAX® SM is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.

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Important Safety Information (cont.)

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those with diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections.
- Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.
- Contact lenses should not be worn when the eyes are inflamed.
- There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

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

Please see brief summary of Prescribing Information on adjacent page.

References: 1. LOTEMAX SM Prescribing Information. Bausch & Lomb Incorporated. 2. Data on file. Bausch & Lomb Incorporated. 3. Cavet ME, Glogowski S, Lowe ER, Phillips E. Rheological properties, dissolution kinetics, and ocular pharmacokinetics of loteprednol etabonate (submicron) ophthalmic gel 0.38%. *J Ocul Pharmacol Ther.* 2019. doi: 10.1089/jop.2019.35(5):291-300.

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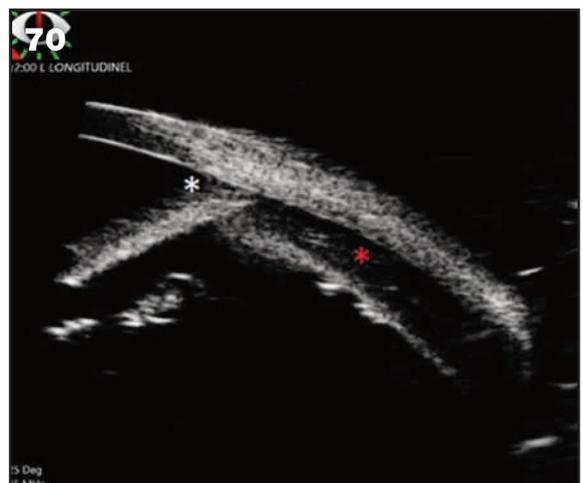
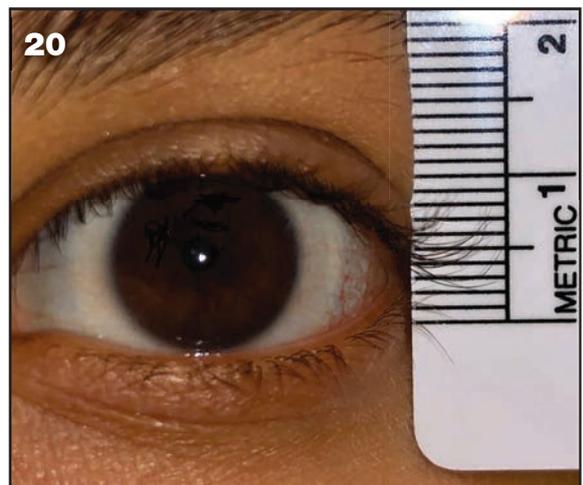
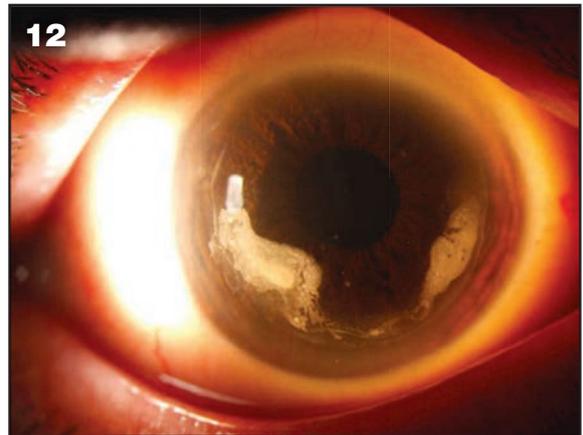
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DURYSTA™
(bimatoprost implant) 10 mcg
For intracameral administration



INDICATIONS AND USAGE

DURYSTA™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION

Contraindications

DURYSTA™ is contraindicated in patients with: active or suspected ocular or periocular infections; corneal endothelial cell dystrophy (e.g., Fuchs' Dystrophy); prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]); absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; hypersensitivity to bimatoprost or to any other components of the product.

Warnings and Precautions

The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ 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.

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

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Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

Adverse Reactions

In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5%-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

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

References: 1. DURYSTA™ [Prescribing Information]. Irvine, CA: Allergan, Inc.; 2020. 2. Data on file, Allergan, 2020. 3. Standing S. Orbit and accessory visual apparatus. In: *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. 41st ed. Philadelphia, PA: Elsevier Limited; 2016:666-708.



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DURYSTA™
(bimatoprost implant) 10 mcg
For intracameral administration

DURYSTA™

(bimatoprost implant) 10 mcg
For intracameral administration

Brief Summary—Please see the DURYSTA™ package insert for full Prescribing Information

INDICATIONS AND USAGE

DURYSTA™ is a prostaglandin analog indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

CONTRAINDICATIONS

DURYSTA™ is contraindicated in patients with active or suspected ocular or periocular infections; corneal endothelial cell dystrophy; prior corneal transplantation, or endothelial cell transplants; absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; or hypersensitivity to bimatoprost or any other components of the product.

WARNINGS AND PRECAUTIONS

Corneal Adverse Reactions: The presence of **DURYSTA™** implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of **DURYSTA™** should be limited to a single implant per eye without retreatment. Caution should be used when prescribing **DURYSTA™** in patients with limited corneal endothelial cell reserve.

Iridocorneal Angle: Following administration with **DURYSTA™**, the intracameral implant is intended to settle within the inferior angle. **DURYSTA™** should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including **DURYSTA™** intracameral implant. **DURYSTA™** 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.

Intraocular Inflammation: Prostaglandin analogs, including **DURYSTA™**, have been reported to cause intraocular inflammation. **DURYSTA™** should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Pigmentation: Ophthalmic bimatoprost, including **DURYSTA™** intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. While treatment with **DURYSTA™** can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Endophthalmitis: Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering **DURYSTA™**, and patients should be monitored following the administration.

ADVERSE REACTIONS

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.

The most common ocular adverse reaction observed in two randomized, active-controlled clinical trials with **DURYSTA™** in patients with OAG or OHT was conjunctival hyperemia, which was reported in 27% of patients. Other common ocular adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, and iritis. Ocular adverse reactions occurring in 1-5% of patients were anterior chamber cell, lacrimation increased, corneal edema, aqueous humor

leakage, iris adhesions, ocular discomfort, corneal touch, iris hyperpigmentation, anterior chamber flare, anterior chamber inflammation, and macular edema. The following additional adverse drug reactions occurred in less than 1% of patients: hyphema, iridocyclitis, uveitis, corneal opacity, product administered at inappropriate site, corneal decompensation, cystoid macular edema, and drug hypersensitivity.

The most common nonocular adverse reaction was headache, which was observed in 5% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no adequate and well-controlled studies of **DURYSTA™** administration in pregnant women to inform a drug associated risk. Oral administration of bimatoprost to pregnant rats and mice throughout organogenesis did not produce adverse maternal or fetal effects at clinically relevant exposures. Oral administration of bimatoprost to rats from the start of organogenesis to the end of lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant exposures.

In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 1770 times the maximum human bimatoprost exposure following a single administration of **DURYSTA™** (based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858).

In a pre/postnatal development study, oral administration of bimatoprost to pregnant rats from gestation day 7 through lactation resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from **DURYSTA™**; based plasma C_{max} and a blood-to plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from **DURYSTA™**; based on plasma C_{max}).

Lactation: There is no information regarding the presence of bimatoprost in human milk, the effects on the breastfed infants, or the effects on milk production. In animal studies, topical bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **DURYSTA™** is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for **DURYSTA™** and any potential adverse effects on the breastfed child from **DURYSTA™**.

Pediatric Use: Safety and effectiveness of **DURYSTA™** in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human exposure [based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858]).

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (1770-times the maximum human exposure, based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858).

PATIENT COUNSELING INFORMATION

Treatment-related Effects: Advise patients about the potential risk for complications including, but not limited to, the development of corneal adverse events, intraocular inflammation or endophthalmitis.

Potential for Pigmentation: Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent.

When to Seek Physician Advice: Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

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Dear Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 2nd-Year Ophthalmology Resident Wet Lab Programs for the 2020-2021 Residency Year in Fort Worth. These programs offer a unique educational opportunity for second-year residents. To better familiarize beginning ophthalmologists with cataract surgery, these programs will consist of both didactic lectures and a state-of-the-art, hands-on wet lab experience. Technology and technique will be explained and demonstrated and surgeons will leave better prepared to optimize outcomes and manage complications when they arise. The programs also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your 2nd Year residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

Sincerely,
Course Directors

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CME courses are restricted to 2nd-year residents enrolled in an ophthalmology residency program at the time of the course. There is no registration fee for this activity. Air, ground transportation in Fort Worth, hotel accommodations, and modest meals will be provided through an educational scholarship for qualified participants.

Physicians

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Review Education Group, LLC. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Credit Designation Statement

This activity has been approved for **AMA PRA Category 1 Credits™**



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Before Enhancing Post-LASIK Patients

Consider updated strategies for flap management, when to operate, communication, epithelial ingrowth and more.

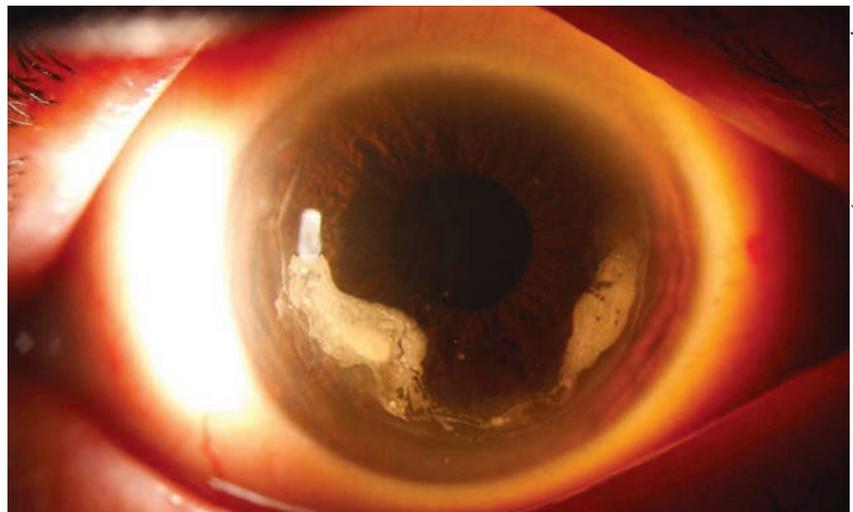
Sean McKinney, Senior Editor

Should you lift the flap or leave it in place? The question continues to divide refractive surgeons when they discuss how to enhance post-LASIK patients. In this update, practitioners weigh in on this issue and discuss other personal approaches, providing insights on the timing of procedures, preop and postop evaluations, epithelial ingrowth, billing and make-or-break ways to ensure that initial imperfections don't prevent you from eventually optimizing vision.

Which Side Are You On?

Edward Manche, MD, division chief of the cornea and refractive surgical service at the Byers Eye Institute at Stanford University School of Medicine, says he typically performs enhancements with a flap lift, when necessary, during the first 12 to 24 months after primary surgery. "Beyond that time frame, I turn to surface ablation," he says. "If you do a lift during the first year or two, the risk of ingrowth is fairly low, about 1 to 2 percent. If you do it beyond that, the incidence increases dramatically.

After determining that an enhance-



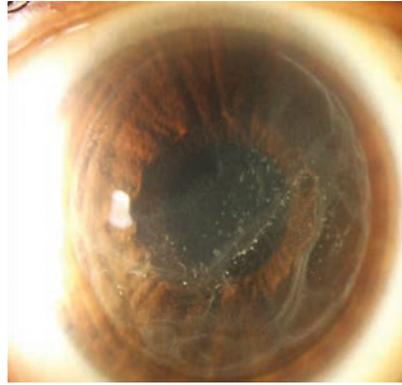
All photos: Edward Manche, MD

Figure 1. Extensive epithelial ingrowth resulted in elevation, opacification and scalloping of the LASIK flap margin in the right eye of of this patient.

ment is indicated, Minneapolis surgeon Elizabeth A. Davis, adjunct assistant clinical professor at the University of Minnesota, says she uses PRK with mitomycin-C over the flap in 99 percent of her cases. "We did a study that demonstrated that nearly one-third of patients who underwent a flap lift experienced epithelial ingrowth," says Dr. Davis. "The only rare time I might consider lifting a flap for an enhancement is if I find epithelial ingrowth

under a flap, creating a refractive error. Then I lift and perform a small enhancement, though you must be careful in those cases because you don't know what the refractive error might be once you remove the ingrowth. I might also consider lifting the flap for a significant hyperopic refractive error because, in my experience, hyperopic LASIK produces a better outcome than hyperopic PRK."

Dr. Davis proceeds with all en-



Figures 2 and 3. Epithelial ingrowth is visible under the flap in the two slides above, reflecting the extensive loss of the overlying flap from the 3 o'clock to 9 o'clock meridians. The cornea on the left reveals diffuse illumination and the cornea on the right shows sclerotic scatter.

hancements only after confirming evidence of post-LASIK stability, as reflected in the refraction and topography. “For LASIK, my general rule of thumb is to enhance no earlier than three months after primary surgery, but it’s one month per diopter of myopia and three months per diopter of hyperopia,” she explains. “So if the patient’s a 1-D myope, I’ll do an enhancement at three months. If the patient’s a 6-D myope, I’ll do it at six months. If the patient’s a 1-D hyperope, it’ll be at three months.”

Deepinder K. Dhaliwal, MD, director of refractive surgery and the cornea service at the University of Pittsburgh Medical Center, says she prefers to lift the flap for enhancements, but only if she was the one who performed the primary surgery and only after meticulously evaluating the patient to determine if an enhancement is needed. “I’m a flap-lifter,” admits Dr. Dhaliwal. “If I’ve created the LASIK flap, I know it’s been created well, either with a microkeratome or a femtosecond laser. I have a special way of lifting the flap, scoring the edge at the slit lamp with a 30-gauge needle and then marking it with a pen. After that, I gently use a Sinsky hook, open the entire flap edge, peel it back and perform the enhancement. We then typically put a bandage contact lens over the eye.

It’s a nice technique—very predictable and reproducible.”

Dr. Dhaliwal says careful assessment is essential to confirm that the patient is a good candidate for an enhancement. “This step is often overlooked,” she adds. “I’ve seen more complications after LASIK enhancements, usually ones referred to me, than after primary LASIK.”

To Enhance or Not

Before performing an enhancement, Dr. Dhaliwal images the cornea to find out what type of flap was initially created. “In the early days of microkeratomes, it was a bit like the Wild West,” she says. “If you’re going to lift, you really have to understand what’s going on. A buttonhole or some other unusual situation could be involved. Then, obviously, the surface laser is going to be a much better option. If the flap is not of good quality and integrity, I treat the surface.”

When she decides to lift the flap, she doesn’t use a wavefront-guided approach. “I want to remove as little corneal tissue as possible,” she explains. “So I offer a conventional laser enhancement. Sometimes, when you attempt a custom treatment, challenging aberrations can result in a lot of tissue ablation. I try to keep it simple.

We have to remember that we’re going in a second time. You want to minimize the risk of ectasia.”

Dr. Dhaliwal says she also holds off on patients who are approaching presbyopia. “They’ll need reading glasses if you take away the mild myopia,” she points out. “We do a contact lens trial to simulate the effect of the enhancement and determine if they really want it.”

When appropriate, Dr. Dhaliwal says she lifts a flap confidently, even years after primary surgery, without risking the development of epithelial ingrowth. “The way we do it, we usually don’t see epithelial ingrowth,” she says. “Of course I’ve had some, but the problem can be eliminated if you identify it early enough. (For strategies for managing epithelial ingrowth, see “After the Surgery” on page 14.)

Preparing for Enhancements

Many surgeons mentally prepare patients for LASIK enhancements before the primary procedure. “If you’re offering surgery to a younger cohort of patients, say 18 to 20 years old, even if they’ve gone one or two years without a change in glasses and their vision is defined as stable by FDA guidelines, that doesn’t mean they won’t experience progression,” says Dr. Manche. “I tell younger patients they’ll likely need additional surgery at some point. I even tell high myopes to wait until after age 30 before undergoing LASIK. Even then, there’s a risk of further progression.”

Dr. Davis prepares LASIK candidates for the eventual need for enhancements if they have high refractive errors—higher levels of myopia, higher levels of astigmatism or hyperopia. “Even though the overall percentage of patients who need an enhancement after LASIK is 5 percent, the risk for these patients may be greater than this,” she observes. “Not only that, if they have a higher refractive error,

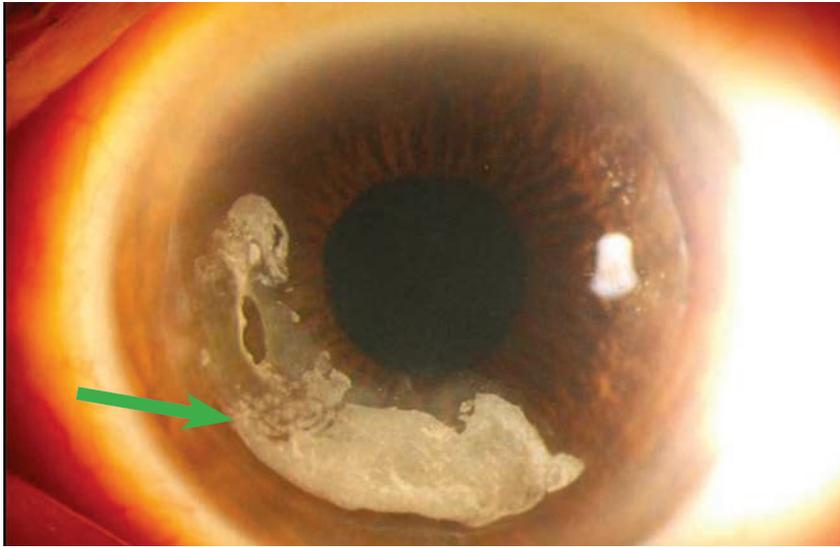


Figure 4. A LASIK flap in the left eye of this patient shows extensive epithelial ingrowth. A 1 x 0.5-mm area of fluorescein reveals pooling, but no staining, consistent with a hole in the flap.

they're going to have to wait longer for an enhancement to achieve stability."

Dr. Manche individualizes his preop patient communication based on the possibility of enhancements. "Our patients go into the first LASIK surgery fully informed," he says. "For example, a preop patient may be at -8 D plus 3.5 D of cylinder. After surgery, the patient may be 20/30, but she understands the need to wait three to six months before we do a touch-up to try to get to 20/20."

Despite clear communication, however, Dr. Manche acknowledges many patients perceive outcomes differently than surgeons do. "When we help a -8 D patient end up at -0.5 D, at 20/25, and then we do a touch-up to get the patient to 20/20 or 20/15, we think, 'Wow, look how well this case turned out.' The patient's view, however, is: 'I had LASIK. It didn't work at first and I had to go back and get it done again.' It's a different perspective that's worth keeping in mind. I also make sure patients understand that I may need to lift the flap or perform PRK in one to two years, even after a perfect initial outcome."

Dr. Davis also recommends a discus-

sion of billing up front. "Surgeons take different approaches to billing," she says. "I feel that, during the first year after surgery, I shouldn't bill for enhancements for patients who aren't on target after the first treatment. However, if we do achieve the target outcome and they come back in one, five or 10 years with changes in their vision that aren't related to the primary surgery,

then we bill them."

Dr. Dhaliwal says some patients have unrealistic expectations. "They might think they've paid for a lifetime warranty, which is promised by many of the discount LASIK providers," she observes. "You may encounter patients who feel 'entitled' to undergo a free enhancement, even though they've had very little education about the risks and benefits of the procedure. I consulted with one patient who developed infectious keratitis after undergoing a LASIK enhancement at one of the discount places. The patient said, 'You know, if I thought there was a risk of infection after an enhancement, I wouldn't have gotten this done.' She felt her vision wasn't that bad before the enhancement. But because she paid for a lifetime guarantee, she decided to take what she could get. So we have to be very careful about offering more surgery to these patients."

After the Surgery

At some point, of course, all surgeons confront the challenges of minimizing or eliminating the threat of postop epithelial ingrowth, which can

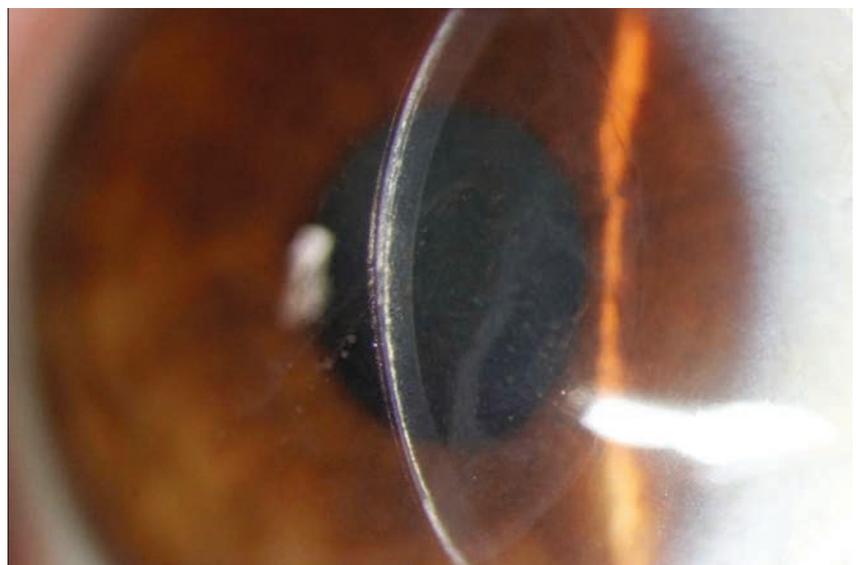


Figure 5. A high-magnification cross-section view of this cornea shows epithelial ingrowth in the flap interface and extensive loss of the overlying flap because of stromal lysis.

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develop after primary surgery *or* after re-lifting the flap.

“In the past, I’ve had to manage patients who’ve developed significant epithelial ingrowth. Basically, when you recognize it, you have to re-lift the flap,” says Dr. Dhaliwal. “However, if it’s mild, less than 1 mm into the stromal surface, if there’s no associated flap melting and if it’s not causing any irregular astigmatism or refractive changes, then I leave it alone. If it’s growing and affecting the patient’s vision, then I’ll lift the flap and deal with the epithelial ingrowth.

“I lift the flap and remove the ingrowth from both stromal surfaces, from underneath the flap and from the stromal bed,” she continues. “Then I replace the flap. I allow a long drying time of five minutes each in these cases, and I suture the flap down if it’s problematic, particularly if it’s the second time I’m lifting the flap. I’ll also use Tisseel fibrin glue (Baxter Healthcare) to keep it down. If it’s a high-quality flap, and I’ve made it myself and I know what’s going on, I prefer to lift it, as I mentioned.”

Although most epithelial ingrowth develops after enhancements, Dr. Manche cautions against overlooking the possibility of it developing after primary surgery. “You’ll see ingrowth in patients who have had complications from the original LASIK surgery, the most common complications being epithelial defects, epithelial sloughs and other issues of that nature,” he says. “If you develop epithelial ingrowth after primary surgery, for whatever reason, in most cases, identification and prompt intervention are critical.”

These patients respond well to a lift-and-scrape technique, he notes. “You don’t need adjunctive therapies,” he says. “In most cases, if you identify epithelial ingrowth in the first month or two, you can just lift the flap and remove the ingrowth mechanically, then replace the flap, and that’s usually curative. Commonly, the location of



Figure 6. A sutured LASIK flap is shown after removal of epithelial ingrowth.

the epithelial defect is where the epithelial ingrowth first develops. If the patient is yours, take meticulous notes after surgery, focusing on the area of the defect. During the first week, epithelial ingrowth is hard to see because it’s relatively transparent, forming almost a little ghost line under the flap. At three to four weeks, though, it starts to become more opaque and much more obvious. You can sometimes see elevation of the flap or—where the flap edge starts to get eaten away—scalloping of the flap. You want to be careful to look at the flap at the slit lamp for these changes. Occasionally, you’ll see changes in corneal topography, but by then the epithelial ingrowth has become fairly advanced. Looking for it early is very important.”

Managing epithelial ingrowth after an enhancement can be more complicated than after primary surgery, Dr. Manche notes. “It tends to be more recurrent than after the primary surgery,” he says. “I see a lot of patients sent to me for second opinions who’ve had either longstanding epithelial ingrowth or who’ve had one or two procedures to remove the ingrowth.”

In these cases, Dr. Manche lifts the flap, removes the epithelial ingrowth and uses adjunctive treatments, such as Tisseel glue or ReSure ocular sealant (Ocular Therapeutix), a polyethylene glycol hydrogel, to secure the flap in place. “In these cases, when you’ve had a recurrence, you really need to use the adjunctive treatments,” he

notes. “I’ve had excellent results with both of those modalities. However, we occasionally get a case in which the epithelial ingrowth recurs even after we’ve used the adjuncts. In such a situation, I’ll suture the flap down. That’s the definitive treatment for epithelial ingrowth.”

Dr. Davis tries to avoid ingrowth at all costs. “I think the risk of epithelial ingrowth has motivated a lot of surgeons to move toward not lifting the flap,” she says. “That’s why more of us are choosing PRK to enhance these patients.” Once epithelial ingrowth takes hold, it can be very difficult to eliminate, she adds, noting, “even when you get rid of it, it tends to grow back and become a recurrent problem.”

In most cases, when she sees epithelial ingrowth, Dr. Davis says she lifts the flap and goes in with an instrument such as a PRK spatula. “I find it comes off easily in a sheet,” she says. “I also remove the epithelium beyond the perimeter of the flap for a couple of millimeters, and then remove the epithelium from the back of the flap when I position it down. I apply Tisseel fibrin glue over the whole surface and put a bandage contact lens over it. What I’m trying to do when using that technique is to give the flap a head start in sealing before the epithelium regrows, approaches the flap junction and dives under the edge of the flap.”

Other Sequelae

Besides epithelial ingrowth, refractive regression and other issues can challenge you after surgery.² “When you’re evaluating a patient for regression, distinguish between progression changes and regression of effect,” says Dr. Manche. “If your patient is young, they may still be experiencing an increase in their axial myopia.”

One way to be sure is to look at topography, he continues. “Let’s say you have a patient you performed LASIK on five years ago and you have yearly

follow-up data. You need to evaluate any changes carefully. If topography shows that the keratometry values were K1 of 44 D by K2 of 44 D preop, K1 of 40 D by K2 of 40 D at one year postop and then K1 of 41 D by K2 of 41 D at five years postop, regression could be due to corneal epithelial hyperplasia. If the K readings are exactly the same as they were five years earlier, then the axial length is increasing, so it's progressive myopia.

"There's a difference," continues Dr. Manche. "If it's progression, and not just regression, you want to make sure the patient is stable. Consider having a couple of measurements many months apart to make sure the patient isn't continually progressing. If it was regression or progression, but now it's stable, I follow my usual protocol for performing an enhancement: At one to two years postop, a flap lift, provided the thickness of the cornea permits it; after two years postop, surface ablation."

Dr. Davis watches closely for regression after PRK. "I'm not aware of any way to prevent it," she says. "I'd say if you're getting a lot of regression, you ought to reassess your treatment nomogram. Rather than basing it on one-month outcomes, perhaps you need to look at six-month or one-year outcomes and adjust the nomogram accordingly."

Says Dr. Dhaliwal: "In terms of regression—as opposed to progression of myopia, or myopic progression due to a cataract—you really have to understand what's going on with your patient. For example, in the case of a postop patient who truly has myopic regression within three months of surgery, if I think the patient was left with a primary undercorrection, then proceeding with an enhancement is reasonable. But to be honest, I have to say we're not really seeing a lot of those cases anymore; our laser technology has gotten so much better."

In terms of progression of myopia



Figure 7. A high-magnification view of LASIK flap sutures.

over time, Dr. Dhaliwal adds, "if it's only a small amount and a patient who's nearing presbyopia needs just a bit of myopic correction for night-time driving, I often tell the patient to hold off. I discuss presbyopia and how he or she may hate wearing reading glasses more than wearing night-driving glasses. Discussing indications for a LASIK enhancement before doing the procedure is important."

Dr. Dhaliwal also emphasizes the importance of avoiding ectasia, a major risk factor associated with enhancements. "You have to be aware of how much thickness is left," she says. "If you don't have the measurements of the stromal bed thickness, look at OCT measurements to understand the actual residual stromal bed thickness. I like to preserve 50 percent of the preop total corneal thickness or 250 microns, whichever is greater."

She recommends the use of a Pentacam (Oculus) or other appropriate imaging technology to rule out elevations of the posterior cornea, such as what's seen in forme fruste keratoconus. "I had a patient referred to me with significant post-LASIK ectasia that got a lot worse after her enhancement," Dr. Dhaliwal recalls. "I later discovered she had pre-enhancement posterior elevation, as evidenced on topography and tomography. So, really, she shouldn't have been referred for an enhancement. That's a very important point. I also tell any patient on whom I'm doing an enhancement to refrain

from eye rubbing postop, obviously, because rubbing the eyes contributes to the risk of ectasia."

When using PRK for LASIK enhancements, Dr. Davis also watches for haze. If she sees it, she typically reduces her steroid treatment. "I don't believe that issue is as common when you enhance a patient by lifting the flap," she notes.

Prepare for Success

In most cases, surgeons say, if managed carefully, LASIK enhancements are effective and meet patient expectations.

"Laser vision correction is highly successful," says Dr. Davis. "The vast majority of cases produce an excellent outcome after a single treatment. But like everything in medicine, there's a Gaussian distribution. Just because 95 percent of patients need only a single treatment, obviously your patient isn't one of them if he or she needs an enhancement. Emphasize that the patient is unique; it's important to say that you can provide overall percentages, but not an individual percentage. There's no way to determine preoperatively if your patient will be an under-responder or an over-responder on an individual basis." **REVIEW**

Dr. Manche is a consultant for Allergan, Avedro, Zeiss and J&J Vision. He also provides sponsored research services for Allergan, Alcon, Avedro, Zeiss, J&J Vision and Presbia. He owns equity in RxSight and Vacu-Site. Dr. Dhaliwal is a consultant for Novartis, J&J Vision, Trefoil, receives lecture fees from Ocular Therapeutix and Starr Surgical and receives grant support Noveome. Dr. Davis reports no relevant commercial relationships.

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IMPORTANT SAFETY INFORMATION

Ulcerative keratitis can occur. Patients should be monitored for resolution of epithelial defects.

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A Review of Blepharoptosis Repair

How the cause of the drooping lid will guide your diagnostic investigation and eventual repair of the problem.

H. Joon Kim, MD, Atlanta

Ptosis of the upper eyelid, or blepharoptosis, though ostensibly a straightforward problem, can actually be a challenge to diagnose and repair, thanks to its many possible causes and the strengths and weaknesses of the various surgical approaches. Here, I'll provide advice on how to evaluate a case of acquired adult blepharoptosis, root out its cause and manage it successfully.

Anatomy

A review of the lid anatomy can help when planning blepharoptosis surgery. Elevation of the upper eyelid is a process controlled by three retractors. The first retractor, levator palpebrae superioris, is a striated muscle in the upper eyelid innervated by the oculomotor nerve and is primarily responsible for opening the eyelid. The second, Müller's muscle, is a sympathetically innervated smooth muscle posterior to the levator and is responsible for about 2 mm of eyelid opening. Finally, the third and weakest retractor is the frontalis muscle in the forehead, which is innervated by the facial nerve, and can indirectly raise the upper eyelid

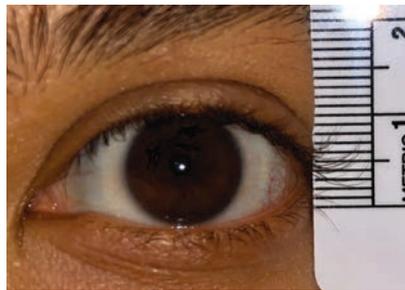


Figure 1. The marginal-reflex-distance 1 (MRD1) is the distance between the center of the pupil and the upper eyelid margin. It averages 4 to 5 mm.

by lifting the eyebrows. Any direct or indirect impact on these muscles can result in blepharoptosis.¹

Classification

Ptosis can result from a number of causes, some of which are quite serious and warrant investigation. The condition can be unilateral or bilateral and can occur in varying degrees of severity that lead to cosmetic and/or functional deficits.

- **Aponeurotic ptosis.** This is the most common form of ptosis, and is due to chronic dehiscence of the levator aponeurosis due to normal aging

changes. It's usually bilateral but is often asymmetric. The changes to the muscle can be accelerated by common events such as long-term contact lens use or intraocular surgery. Despite the severity of the ptosis, the levator function often remains normal.²

- **Myogenic ptosis.** This form of ptosis stems from a myopathy, with the most common diagnoses being a chronic progressive external ophthalmoplegia (CPEO), myasthenia gravis, myotonic dystrophy or oculopharyngeal-muscular dystrophy (OPMD). The myopathy typically progresses, with worsening ptosis correlating with a decrease in levator function. The exception is myasthenia gravis, which is characterized by a fluctuating ptosis with variable levator function. These myopathies also tend to be associated with a constellation of systemic findings, such as a heart block along with CPEO in Kearns-Sayre syndrome, and dysphagia and proximal limb weakness with OPMD.³

- **Neurogenic ptosis.** This variety is uncommon but can signal a serious underlying issue. It can stem from a problem of the oculomotor nerve most commonly due to ischemia from

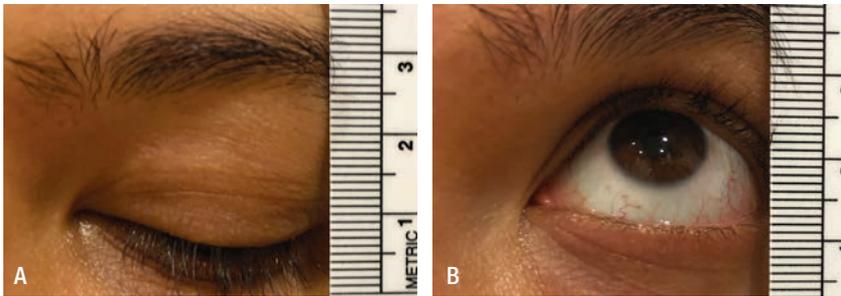


Figure 2. The levator function is measured by the full excursion of the upper eyelid from downgaze (A) to upgaze (B). It should be between 10 and 15 mm.

diabetes, but can also indicate an aneurysm, stroke or tumor. A congenital or acquired form of Horner syndrome can also result in mild ptosis from Müller's muscle being affected, and can be a manifestation of a stroke, tumor (including pulmonary tumors) or vascular disease. Aberrant regeneration of the facial nerve can result in a synkinetic ptosis associated with perioral contraction. A number of supranuclear conditions can also result in neurogenic ptosis as well, such as strokes, multiple sclerosis and brain injury.^{4,6}

- **Mechanical ptosis.** This results from lesions in the lid either weighing it down or preventing it from lifting. Examples of such lesions include eyelid malignancies and symblepharon formation secondary to ocular cicatricial pemphigoid and Stevens-Johnson syndrome.³

- **Traumatic ptosis.** Traumatic ptosis can result from a variety of direct or indirect mechanisms, the most obvious being direct laceration of the lid muscles and nerves. It can also arise from blunt trauma, edema or hemorrhage that causes dehiscence of the levator.⁷

Evaluation

A proper evaluation of the blepharoptosis patient includes a good history, clinical exam and an appreciation for what I call the eyelid "vital signs."

- **History.** Patients with ptosis often report both cosmetic and functional complaints. Ptosis can diminish the peripheral visual field and can result in

difficulty with daily activities of living. The "drowsy" appearance and the aging effect of ptosis are also bothersome for patients, especially if the case is asymmetric. The age of onset and the duration of the ptosis are also important, since they can indicate a more serious underlying problem. In such cases, seek out associated symptoms, such as diplopia, diurnal variation and trouble swallowing. Take a thorough ocular and medical history of the patient and the family, and note any history of surgery or trauma.

- **Clinical exam.** A full ophthalmic exam is warranted, watching for anomalous head positioning, facial asymmetry, synkinesis and abnormal speech. Neutralize any frontalis excursion to eliminate raised eyebrows so you can accurately assess the eyelid position.

Evaluate the acuity and pupil, paying special attention to the presence of anisocoria. Watch for strabismus in primary gaze and perform a thorough motility exam. Note other signs, such as Cogan's lid twitch (overshooting of the upper lid from downgaze to upgaze) and von Graefe's sign (lagging of the upper lid on downgaze). Rule out fatigable upgaze, supplementing your exam with an ice test if there's a high level of suspicion for myasthenia gravis. Assess any proptosis or enophthalmos with an exophthalmometer, and perform a slit lamp exam, looking particularly for signs of dry eyes. Postpone your dilated fundus exam until you've done a full lid exam, since dilating eye drops (i.e., phenylephrine) can

temporarily raise the lid position.

- **Eyelid "vital signs."** The vertical palpebral fissure (the distance between the upper and lower lid margin) should be approximately 10 mm. The normal position of the upper lid margin is about 0.5 mm to 2 mm below the superior limbus. The marginal-reflex-distance 1 (MRD1) is the distance between the center of the pupil and the upper eyelid margin and averages 4 to 5 mm (Figure 1). The levator function is measured by the full excursion of the upper lid from downgaze to upgaze and should be between 10 to 15 mm (Figures 2A and 2B). Deviations from these average values confirm the presence of ptosis; an evaluation of the levator function can help to narrow down the etiology.⁸

- **Ancillary testing.** Initiate a workup if the underlying etiology is unclear. A basic workup can include a comprehensive metabolic panel, complete blood count, erythrocyte sedimentation rate and C-reactive protein. Thyroid function panel and acetylcholine receptor antibodies are common workups if thyroid disease and/or myasthenia gravis are suspected. In cases where a myopathy like CPEO is suspected, you can perform genetic testing, electromyography or even muscle biopsy. If orbital signs are present, including an abnormal pupil exam or other cranial neuropathies, neuroimaging may be in order. You can also order CTA or MRA if you suspect an aneurysm.³ If you suspect Horner syndrome, perform pharmacological testing as well.⁵

Non-surgical Treatment

Some cases of blepharoptosis don't need surgery, and are better treated with the following approaches.

Observation is an acceptable response to entities such as traumatic ptosis or some forms of neurogenic ptosis (e.g., oculomotor palsy from ischemia), which can improve sponta-

neously. Observation can also be appropriate in cases of aponeurotic ptosis that don't yet bother the patient.

Some cases respond best to a pharmacologic treatment. You should have optimal titration of systemic medication in myasthenia gravis patients and stability in thyroid patients prior to surgery. In cases of aberrant regeneration of the facial nerve resulting in synkinetic ptosis, botulinum toxin to the orbicularis oculi can improve the ptosis.⁶⁶

Surgery

Ptosis repair can be classified into anterior and posterior approaches.⁹ The etiology, severity of ptosis, and levator function will often determine the most appropriate method. Regardless of the technique, ptosis repair can be performed in the office setting with local infiltrative anesthesia, or in the operating suite, the latter typically involving sedation.

The anterior approaches consist of:

- **External levator advancement.**

This is the most common procedure. Though it can address a wide range of ptosis, it relies on the presence of a functioning levator. In the procedure, the surgeon advances the attenuated or dehiscenced levator musculo-aponeurotic junction inferiorly onto the superior border of the tarsus.¹⁰ Small-incision techniques can offer the benefit of minimal scarring,¹¹ but a traditional incision allows you to perform a simultaneous blepharoplasty (Figure 3).

- **Frontalis suspension.** This procedure is a great option when there's minimal or no levator function.¹² It allows you to bridge the frontalis muscle to the superior tarsal plate so that raising the brows will result in a more successful elevation of the lid. The bridging material can be autoplasmic (i.e., autogenous tensor fascia lata) or alloplastic (i.e., silicone rods, aloderm). Alloplastic materials, especially silicone rods, are most widely used in adults due to their ease of placement



Figure 3. Preoperative (A) and one month postoperative (B) clinical photos following an external levator advancement.

and adjustability.¹³

If you feel a posterior approach would be better, consider:

- **Müller's muscle conjunctival resection (MMCR).** This requires excellent levator function and is ideal for mild degrees of ptosis (1 to 2 mm). It does, however, require preoperative phenylephrine testing to ensure the viability of the Müller's muscle and the ideal candidacy for MMCR. MMCR would be indicated if you measure 1 to 2 mm of elevation of the upper lid 10 minutes after instillation of 2.5% phenylephrine. Surgical resection ranges between 6.5 and 9.5 mm, following the 4:1 rule: Perform 4 mm of resection for every 1 mm of elevation.¹⁴⁻¹⁶ MMCR remains a popular choice for mild ptosis because it's easy to perform and its results are predictable. Also, patients like that it doesn't result in a visible scar. However, conjunctival scarring and contour issues can be problematic.

- **Fasanella-Servat procedure.**

This procedure involves resection of the conjunctiva, Müller's muscle and the superior border of the tarsal plate.¹⁷ The surgeon usually performs 1 mm of lift for every 2 mm of tarsectomy or 2 mm of conjunctival-Müller resection.¹⁸ It, too, offers the benefit of avoiding a scar. However, tarsal instability and resection of accessory lacrimal glands often lead to dry eye, so this procedure has fallen out of favor.^{19,20}

Both anterior and posterior approaches are very successful in elevat-

ing the lid in the appropriate setting. Eyelid swelling, bruising, and varying degrees of discomfort are to be expected during the immediate postoperative period. Common complications include overcorrection, undercorrection, asymmetry and contour issues, thus making it one of the most challenging surgeries.^{3,12}

In conclusion, though the cause of a patient's blepharoptosis can be challenging to pin down, and you have to weigh the pros and cons of several surgical approaches, a thorough exam and careful surgery can usually help you achieve good results. **REVIEW**

Dr. Kim is an associate professor of Oculoplastics, Orbital and Cosmetic surgery at Emory University in Atlanta.

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INDICATION AND USAGE

DEXYCU[®] (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

- Prolonged use of corticosteroids, including DEXYCU, may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision
- Steroids should be used with caution in the presence of glaucoma

Delayed Healing

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids

Exacerbation of Infection

- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures

WARNINGS AND PRECAUTIONS (cont'd)

Exacerbation of Infection (cont'd)

- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection

Cataract Progression

- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

ADVERSE REACTIONS

- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

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

**DEXYCU (dexamethasone intraocular suspension) 9%,
for intraocular administration
Initial U.S. Approval: 1958**

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

1 INDICATIONS AND USAGE

DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

Prolonged use of corticosteroids including DEXYCU may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

5.2 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids.

5.3 Exacerbation of Infection

The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection.

5.4 Cataract Progression

The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Increase in Intraocular Pressure [see *Warnings and Precautions* (5.1)]
- Delayed Healing [see *Warnings and Precautions* (5.2)]
- Infection Exacerbation [see *Warnings and Precautions* (5.3)]
- Cataract Progression [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trials Experience

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

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively [see *Data in the full prescribing information*].

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use

Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use

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

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

Smoking's Influence on Wet AMD Treatment

Smoking has a number of negative effects on the body, and a recent study indicates that it may contribute to worse visual outcomes as well. A research team investigated the effect of smoking status on the one-year visual outcomes in eyes treated with anti-VEGFs for nAMD.

Their retrospective, observational analysis included 987 treatment-naïve eyes of 837 patients with nAMD. Smoking status was documented at baseline; anti-VEGF therapy took place over a period of 11 years, from January 2006 to December 2016.

The researchers reported a significant difference in mean improvement in visual acuity at 12 months between nonsmokers, ex-smokers and current smokers (7.7 vs. 6.1 vs. 3.5 letters; $p=0.046$). The median number of anti-VEGF injections over the 12 months was not significantly different by smoking status, and the researchers noted that current smokers were on average 6.2 years younger than nonsmokers when starting treatment.

Additionally, the analysis of smoking effects on nAMD treatment outcomes revealed significant differences

between smoking groups for baseline VA and baseline choroidal neovascular membrane size. Current smokers have an up to sevenfold greater risk of developing nAMD than nonsmokers,

and despite being younger, the researchers noted that these patients tended to have more aggressive disease with worse baseline VA and larger CNVM. Nonsmokers also had more than twice the gain in VA after a year.

The researchers concluded that patients who continued to smoke while undergoing anti-VEGF therapy for nAMD experienced inferior 12-month and 24-month visual outcomes. The mechanism of association between current smoking and poorer visual outcomes with anti-VEGFs is unclear, but the authors suspect a genetic component may influence nAMD treatment outcomes.

Retina 2020;40:1696-1703.
Vittorio AF, Nguyen V, Barthelmes D, et al.

Quantifying IOP Reduction after Cataract Surgery

A retrospective study conducted

by researchers in Portugal and the United Kingdom sought to define the extent of intraocular pressure reduction caused by uncomplicated cataract surgery in individuals with glaucoma vs. those with healthy eyes, to guide physicians hoping to use cataract surgery as an intervention for glaucoma. (The authors note a lack of data in the literature covering this topic in eyes with intraocular pressure measurements below 30 mmHg and open angles.) They hoped to contribute to the eventual creation of a formula that would allow physicians to predict intraocular pressure reduction using basic demographic and clinical measures.

Data from surgeries performed at eight sites in the United Kingdom between January 2006 and May 2015, involving 22,831 eyes—20,580 healthy eyes and 2,251 eyes with glaucoma—were analyzed. Eyes with intraoperative complications, extreme axial lengths, baseline IOP below 6 mmHg or above 20 mmHg, or other pathologies (with the exception of amblyopia), or that were undergoing multiple procedures, were excluded. (The authors note that information regarding glaucoma subtypes, topical medication use and previous glaucoma surgery was not available.)

In healthy eyes the mean IOP reduction was 1.4 ± 3.74 mmHg; in glaucomatous eyes the mean reduction



was 1.03 ± 5.02 mmHg. Analysis using multiple linear regression found that factors associated with amount of IOP reduction included preoperative IOP, preoperative corrected visual acuity, age, axial length and a diagnosis of glaucoma. The authors conclude that in glaucomatous eyes not differentiated by degree of angle closure or other contributory factors, phacoemulsification alone produces only a modest reduction in IOP—an amount that may not be clinically meaningful.

J Glaucoma 2020;29:8:689-93
Leal I, Chu CJ, Yang YY, et al.

Follow-up in Proliferative Diabetic Retinopathy Care

An unprecedented study of interrupted treatment of proliferative diabetic retinopathy has found that 61 percent of patients with shared risk factors, such as not speaking English as a primary language and being 56 years old or older, were lost to follow-up treatment for more than six months at least once. Previous studies found this level of non-compliance in only 28.8 percent and 25.4 percent of patients.

The findings resulted from a retrospective cohort chart review of 418 adult patients with PDR who had been treated with intravitreal anti-VEGF injections and/or panretinal photocoagulation between January 1, 2014, and June 1, 2018, at the Boston University School of Medicine. Only 5 to 10 percent of patients have been lost to follow-up in clinical trials, the study noted.

A multivariate analysis identified the following risk factors for the studied patients: Non-English as the primary language (odds ratio [OR], 1.83; $p=0.006$); age 56 to 65 years old (OR, 1.86; $p=0.014$); age older than 65 years compared to age 55 years or younger (OR, 1.94; $p=0.027$); living 20 miles or less from the institution (OR, 2.68;

$p=0.009$); having more than five comorbidities (OR, 2.38; $p=0.034$); seeing 20 or more distinct departments (OR, 4.66; $p=0.007$); missing more than 10 percent of non-eye-care appointments (OR, 1.61; $p=0.038$) and receiving only panretinal photocoagulation compared to only anti-VEGF therapy (OR, 1.93; $p=0.031$).

The study authors say that, to date, this is the most comprehensive study examining risk factors for LTFU (lost to follow-up) in patients being treated for proliferative diabetic retinopathy. They note that many of the variables assessed in this study have not been examined in this context previously. Besides primary language, some of these variables included history of mental illness and substance abuse, homelessness and food insecurity, insurance type, and history of noncompliance and missed appointments in other settings. Additionally, the study reported a disparity between the use of anti-VEGF therapy and panretinal photocoagulation. When comparing anti-VEGF agents to PRP, landmark studies have established ranibizumab monotherapy and aflibercept to be non-inferior and superior, respectively, the researchers observed. However, this study shows that these findings often don't match findings in the clinical environment.

Identifying patients at high risk for being lost to follow-up may help in choosing treatment modality and appropriate patient counseling, the study concluded.

Am J Ophthalmol 2020;216:18-27.
Green M, Tien T, Ness S.

Microvascular Impairments in Non-DR Diabetic Patients

Researchers used optical coherence tomography angiography to evaluate microvascular impairments in the eyes of diabetic patients with no diabetic retinopathy, as part of a systematic review and meta-analysis.

They searched PubMed and Embase databases to identify studies using optical coherence tomography angiography to compare microvascular changes between diabetic eyes without clinical retinopathy and healthy controls. They extracted and analyzed data of interest using Review Manager V.5.3 and Stata V.14.0. They used weighted mean differences and their 95% confidence intervals to assess the strength of the association.

Forty-four cross-sectional studies involving 2,221 diabetic and 1,838 healthy eyes were included.

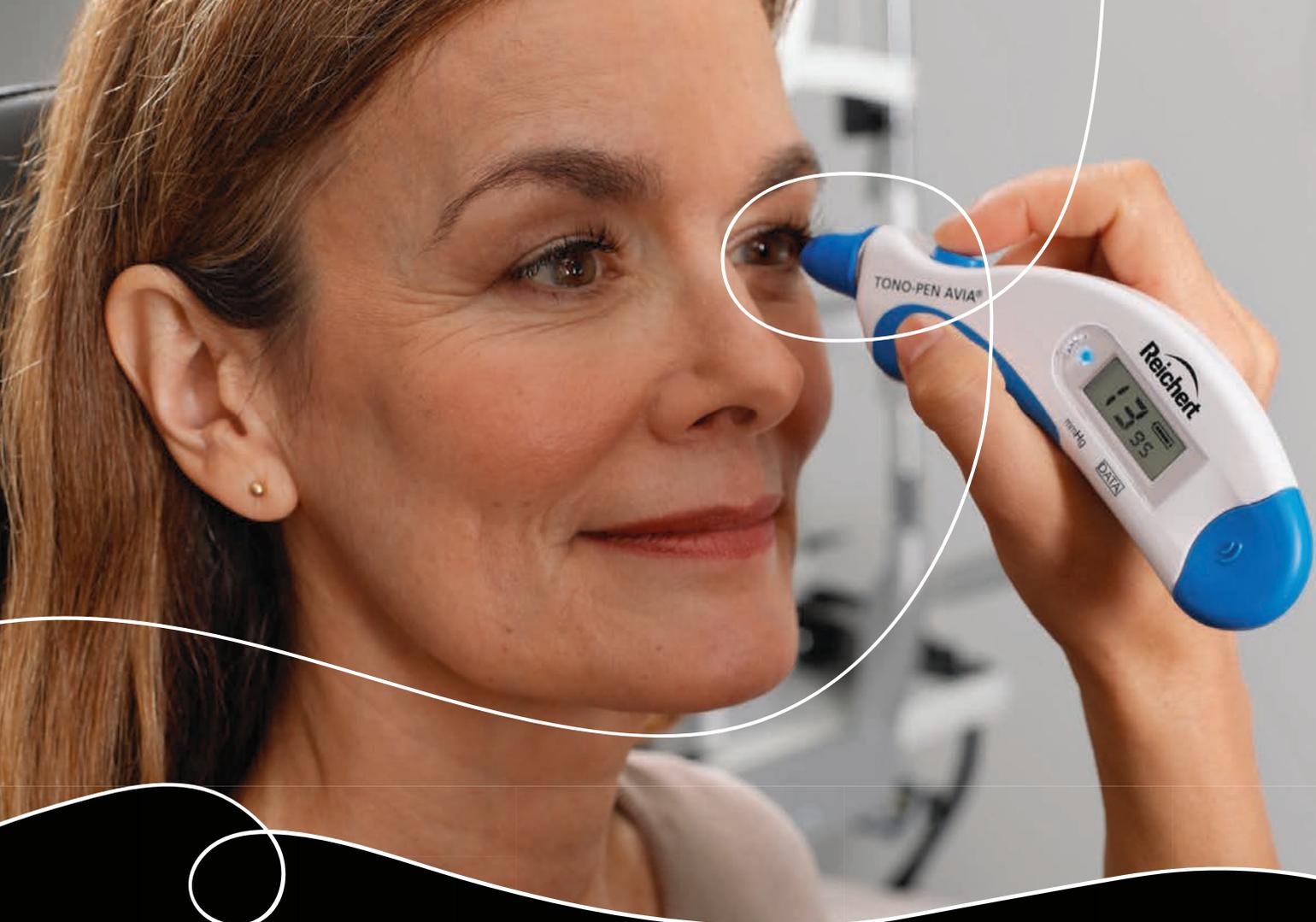
Here are some of the study's findings:

- OCTA imaging revealed that, when compared to the healthy control group, the no-diabetic-retinopathy group manifested enlarged areas and increased perimeters of the foveal avascular zone, with decreased perfusion density in the superficial and deep capillary plexus of the macula (except parafoveal perfusion density of the inner retina and foveal perfusion density) and reduced radial peripapillary capillary perfusion density values.

- In addition, subgroup analyses according to the type of diabetes mellitus indicated that most of those differences became nonsignificant (except parafoveal PD in the deep capillary plexus) in type 1 diabetes mellitus, while in type 2 diabetes mellitus, they remained statistically significant.

The researchers wrote that their findings suggested that retinal microvascular impairments might have occurred prior to clinically visible diabetic retinopathy and could be detected early by optical coherence tomography angiography. However, they added, those manifestations could be inconsistent depending on the type of diabetes mellitus. **REVIEW**

Am J Ophthalmol 2020; Sept 31.
[Epub ahead of print].
Zhang B, Chou Y, Zhao X, et al.



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Corneal Ulcers: Workup & Treatment

Christine Leonard, Associate Editor

Corneal specialists share their diagnostic tips, and discuss culturing techniques and treatments.

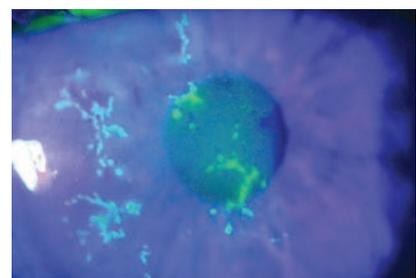
Though the most common culprits behind corneal ulcers are usually bacterial, atypical agents like fungi and protozoa can masquerade as a seemingly run-of-the-mill red eye and cause endless complications down the line if not brought to heel with the proper course of therapy.

Treating a corneal ulcer starts with correctly identifying the causative organism, and that involves a combination of approaches. Here, experts share diagnostic tips, and explain how and when to culture and which treatments you should reach for.

Narrowing Down Etiologies

“Corneal ulcers can present in very different forms and colors,” says Sophie Deng, MD, PhD, professor and Joan and Jerome Snyder Chair in Cornea Diseases at the Stein Eye Institute at the University of California, Los Angeles. “But looking at the cornea alone can be misleading. Textbooks will say that fungal infections have feathery edges, but we see this characteristic all the time in microbial infections as well. Using a combination of presentation, patient history and a consideration of the various risk factors will help to guide you.”

A thorough patient history that in-



Sophie Deng, MD, PhD

Figure 1. An eye with herpetic zoster reactivation. The dendritic ulcer is a classic feature of herpes infections.

cludes information about lifestyle, hygiene and occupation will often clue you in to the types of infections the eye is most susceptible to. “Risky behavior, recent trauma, a history of herpes in the eye, duration of symptoms, an abrupt or gradual onset, and prior therapy before seeking care are all important to ask about,” says Kathryn Colby, MD, a professor and chair of the department of ophthalmology at New York University.

Marjan Farid, MD, a clinical professor of ophthalmology at the University of California Irvine, offers some examples. “An agricultural worker may be at greater risk for a fungal infection because of exposure to soil and plant material,” she explains. “A contact lens wearer who’s been sleeping in their contact lenses or has poor contact lens hygiene is at a higher risk for *Pseudo-*

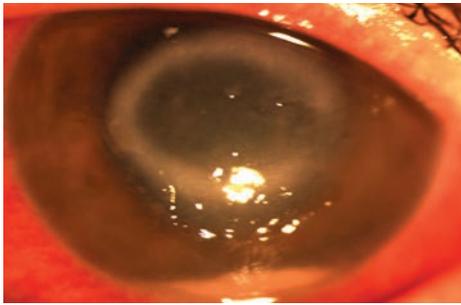


Figure 2A. This patient has *Acanthamoeba* and a fungal ulcer in the same eye.

monas corneal ulcers. And if they've gone into fresh water wearing their contact lenses or wash their contact lenses with water instead of contact lens solution, they're at risk for *Acanthamoeba* infection.

"Herpes-related keratitis is also very common in this country," Dr. Farid continues. "A large percentage of the population has the herpes virus in their body. It manifests in times of stress, but herpetic outbreaks in the eye will manifest in only a small percentage of people. The outbreaks can be epithelial, stromal or endothelial. Epithelial keratitis is not uncommon and has a specific type of presentation—usually a dendritic pattern on the ocular surface (Figure 1). That pattern will clinch a diagnosis, but sometimes herpes can present more atypically. We always have to consider herpetic disease when we see epithelial ulcerations of the cornea."

Dr. Colby adds that a history of present illness in addition to the medical history is also something to take under consideration. "Your patient may have coexisting diseases that could impact your diagnosis," she says. "Do they have a history of diabetes or are they immunosuppressed for any reason? These types of patients will be at higher risk for almost any infection."

Autoimmune diseases, when not well-controlled systemically, can cause significant inflammation of the blood vessels of the ocular surface. "The tear film may also be inflamed, and the patient may develop corneal melt, result-

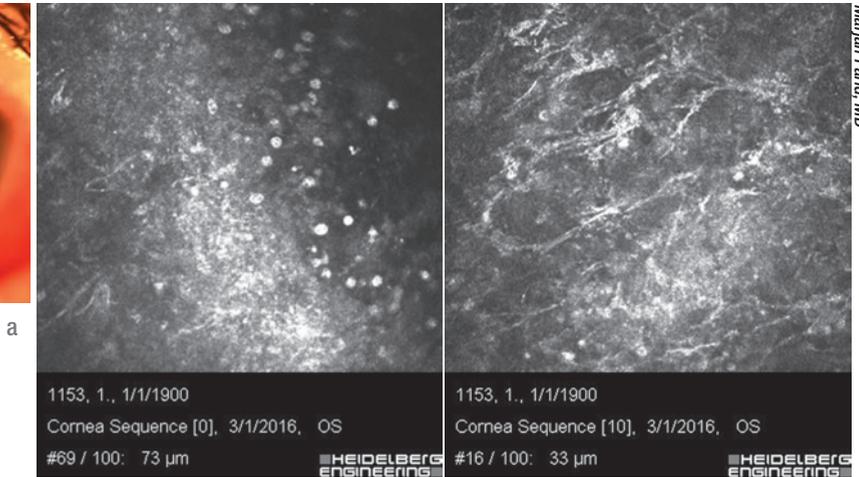


Figure 2B. *Acanthamoeba* cysts (left) and hyphae fungal elements (right) on confocal microscopy. Using confocal microscopy to image the cornea may allow you to jump-start treatment by positively identifying the causative organism while you wait for the pathology results to come back.

ing in thinning of the cornea," says Dr. Farid. "The patient may also develop secondary bacterial infections."

For suspected fungal infections and *Acanthamoeba*, confocal microscopy, if available, can help make the diagnosis (Figure 2). "Confocal microscopy enables us to see organisms in the different layers of the cornea," Dr. Deng says. "Fungal and *Acanthamoeba* cultures take quite a bit of time to come back from the lab, but we can image the patient in the meantime to see whether a fungal infection can be ruled out." She adds that sometimes imaging isn't sensitive enough to detect the organism in its early stages, but the organism may show up on a second, later imaging.

"When In Doubt, Culture"

Dr. Colby notes that you need to do the cultures in a way that will provide you with the information you want.

You'll want to culture large, central corneal ulcers, as well as large peripheral ulcers, she says. You may not need to culture smaller peripheral ulcers that are less vision-threatening and have a fairly clear history—for example, a contact lens wearer with redness and discomfort in one eye for

a few days and a very small peripheral ulcer. "I usually start these patients on a fourth-generation fluoroquinolone broad-spectrum antibiotic and see them the next day," Dr. Farid says. "If they've responded already, I know we're on the right track. Those will usually clear within a few weeks without needing a culture, so those are the only times I don't culture. Most other times, I'll culture a corneal infection so we can get a diagnosis before we start the patient on therapy."

About 15 minutes before she cultures, Dr. Colby removes the proper culture plates from the refrigerator to allow the media to come to room temperature. Most centers have standard culture kits that include media plates for fungal, bacterial, *Acanthamoeba* and viral material (Figure 3). (See table on page 31.) "I generally don't culture for virus, because it's predominantly a clinical diagnosis," Dr. Colby notes.

The next step is to anesthetize the eye with a numbing agent like proparacaine 0.5%, or any topical anesthetic available in the office to ensure the patient is comfortable. Then, carefully swab or scrape the cornea with light pressure at the edge of the ulcer where the concentration of microorganisms is highest. The sharp edge of

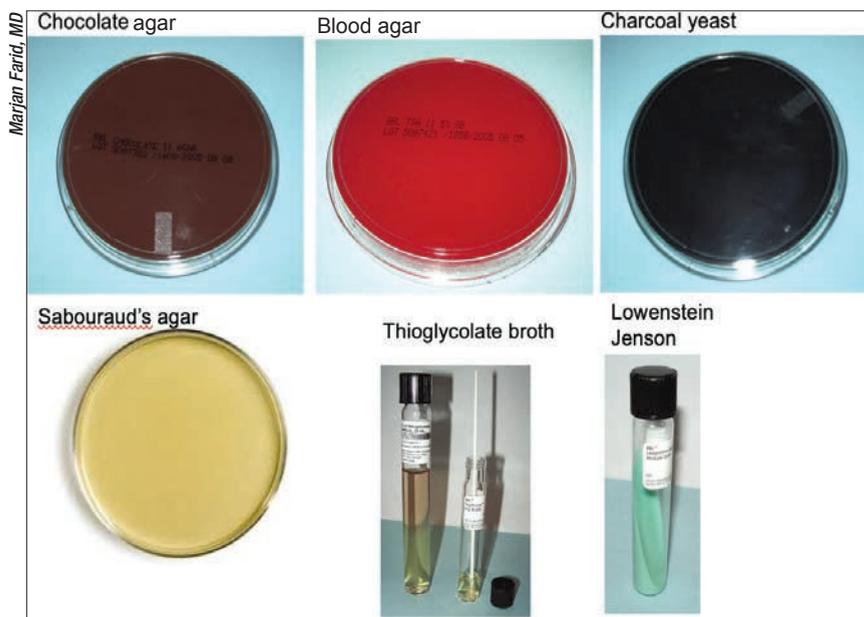


Figure 3. Culture media. When inoculating the culture plate, use regular C-shaped streaks to ensure the culture can be differentiated from any possible contamination on the plate.

an instrument should be tangential to the surface of the cornea to reduce the likelihood of perforation, and you should only move the blade in a single direction.¹

The order in which you swab and plate the culture matters, says Dr. Deng. “Your first sample from the cornea will have the most microorganisms,” she explains. “If the lesion is very small, there may be very little organism left to collect for subsequent swabs. Because of this, you’ll want to plate your first culture on the media with the most nutrients—the chocolate agar for suspected bacterial ulcers—for the best chance of a good analysis. Initially, we’d been plating on the blood agar media first, but in our annual lecture from the microbiology lab a few years ago, they instructed us to use the chocolate agar plate first.”

Some corneal infiltrates are more accessible than others, but there are multiple collection techniques you can try. For easily accessible infiltrates, Dr. Farid says a calcium alginate swab may be used to procure a culture sample. Deeper infiltrates may require a blade for scraping, such as a Kimura spatula.

“If it’s very deep or on the posterior stroma, I pass a braided suture like an 8-0 Vicryl through the infiltrate,” she says. “The microorganisms stick to the suture material, which I culture.” Fungal and protozoal infections may require such sampling from the deeper stromal layer of the cornea.²

When plating your samples, experts say to use regular, recognizable patterns to ensure accurate lab results. “I inoculate the plates using a series of streaks in the shape of a C,” explains Dr. Colby. “You want to inoculate the plate in such a way that the lab will be able to tell if the plate is contaminated, versus if you actually inoculated it. If you use random squiggles, sometimes it can be harder to tell.

“After I’m done with the plates, and the cornea’s been roughed up a bit, I’ll do my smears and stains, which again are done at the edge of the infiltrate and with a blade, such as a sterile Bard-Parker blade. I put them on slides for Gram and Giemsa staining, and occasionally some other specialized stains, depending on what I’m concerned about.

“The stains can sometimes show

you something as soon as it’s been done, but that won’t tell you whether the organisms are dead or not,” she continues. “If someone has bacterial keratitis and it’s been treated or partially treated, you might still recover or see organisms on the stain but not necessarily grow anything on the culture. Generally, bacterial cultures will start to show growth within 24 to 48 hours. Fungal cultures take a bit longer for a definitive result, and *Acanthamoeba* also take longer because of the way the organisms need to be isolated.”

Negative smears may result from an insufficient sample yield, poor staining techniques, prior use of antimicrobial agents, mechanical damage to the cell wall, failure to examine the whole slide or excessive heat fixation.¹ Likewise with Gram staining, difficulties can present if there’s a low yield of organisms to begin with. Deposits of melanin, sodium chloride, talcum powder and precipitated gentian violet may also appear as artifacts, making it harder to identify the causative organism.¹

“If there’s ever any thought: should I or shouldn’t I? Go ahead and culture,” says Dr. Farid. “You’ll never regret culturing. If you decide to culture after starting treatment, the risk of a false negative is higher because your patient is partially treated and getting a good sample is harder. When in doubt, culture.”

Treatment Options

A broad-spectrum antibiotic, especially if you’re not sure what’s growing yet, is a good starting point, since most corneal ulcers you’ll see are likely bacterial. “Most ulcers will get better with a broad-spectrum fluoroquinolone, even if they’re not specifically sensitive to that,” says Dr. Colby. “For example, though the broader spectrum fluoroquinolones have less efficacy against something like a Gram-positive, for which you could give something specifically targeted, we can give antibiot-

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Culture Media	Specificity
Blood agar	Most bacteria and fungi. Excludes <i>Haemophilus spp.</i> , <i>Neisseria spp.</i> , and <i>Moxarella spp.</i>
Chocolate agar	Fastidious bacteria, aerobic bacteria, <i>Haemophilus influenzae</i> , <i>Neisseria spp.</i> , and <i>Moxarella spp.</i>
Lowenstein-Jensen media	<i>Mycobacteria spp.</i> , <i>Nocardia spp.</i>
Loeffler's media	Corynebacteria
Sabouraud's dextrose agar	Fungi, especially <i>dermatophytes</i>
Potato dextrose agar	Fungi
Brain-heart infusion	<i>Streptococci spp.</i> , <i>Meningococci spp.</i> , yeast, fungi
Thioglycolate broth	Aerobic and anaerobic bacteria
Cooked meat broth	Anaerobic and fastidious bacteria
Non-nutrient agar with <i>E. coli</i>	<i>Acanthamoeba</i>
Viral transport	Viruses (e.g., HSV), <i>Mycoplasma spp.</i> , <i>Ureaplasma spp.</i> , and <i>Chlamydia spp.</i>

ics frequently enough to get a very high concentration on the ocular surface. I never start a staph ulcer on moxifloxacin, but the reality is that most staph ulcers would get better with moxifloxacin, simply because there's such a high concentration of medication."

For smaller, peripheral ulcers, Dr. Farid says she often uses a monotherapy of a fourth-generation fluoroquinolone like moxifloxacin, or besifloxacin, which has better MRSA coverage. "If it looks aggressive and central, I may start the patient on fortified antibiotics such as vancomycin or tobramycin," she says. "Those drops usually need to be compounded. Initial treatment for most ulcers is hourly antimicrobial drops. We see these patients almost daily until we see a treatment response and know they're improving. During this time, we also monitor for corneal thinning and perforation.

"If the culture results come back as fungal, or if the history is very indicative of fungal ulcer, then we may start the patient on natamycin eyedrops," Dr. Farid continues. "If I suspect *Acanthamoeba* or if the cultures come back as *Acanthamoeba*, I start the patient on *Acanthamoeba* triple therapy." The classic triple therapy consists of chlorhexidine 0.02%, polyhexamethylene biguanide (PHMB) 0.02% and Brolene 0.1%.

All corneal specialists have their

own practice patterns, but Dr. Colby recommends waiting for a positive confirmation of *Acanthamoeba* before initiating treatment, since the therapy process is very long and painful for the patient. Other corneal specialists recommend initiating treatment immediately, before cultures return from the lab, to prevent its possible progression as much as possible.

Atypical agents such as filamentous fungi and *Acanthamoeba* are especially difficult to treat because there's often a delay in diagnosis, which allows the infection more time to work its way into the cornea (*Figures 4 and 5*). "*Acanthamoeba* keratitis is often initially treated as herpes, and it's also not generally treated first by corneal specialists, but in the community," Dr. Colby says. "It's best if you catch *Acanthamoeba* when it's still superficial in the cornea. When it gets into the stroma, it becomes very difficult to eradicate. Often, patients present with a red eye and are given TobraDex, a combination of tobramycin and dexamethasone, and then when they don't ultimately improve, they're referred for herpes. I recently had a patient who received these different diagnoses, and by the time she got to me, it was clear it was *Acanthamoeba*, but at that point it wasn't medically manageable and we had to do a therapeutic keratoplasty."

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Steroids

When you know definitively which infection you're treating, steroids can help to control inflammation. However, experts caution that steroids can worsen an infection if started too early, especially in the case of fungal keratitis, *Acanthamoeba* or herpes, when prematurely suppressing the body's immune system can have serious consequences.

"We want to culture first, get the patient started on the correct therapy and make sure we're actually killing the microorganisms before starting steroids," Dr. Farid says. "When I feel that I have control of the infectious organism, then I'd consider starting steroids." However, Dr. Farid warns that you should still be cautious. "I like to see the patients on steroids back more frequently initially, to make sure they're not getting worse on the steroids."

"When you look at the randomized trials that have been done on steroids and bacterial keratitis, the steroids really didn't have a dramatic effect," Dr. Colby notes. "However, in a severe ulcer they can be helpful in quelling the inflammation, since a lot of the damage in those cases is from the immune response itself. Again, individual surgeon practice patterns differ, and some start antibiotics and steroids together for corneal ulcers, but that's generally not what I do. I like to make sure I'm not dealing with a fungus. I like to wait until I have 24 to 48 hours of the antibiotic onboard before giving a steroid, if I'm going to give one."

Dr. Colby adds that you should always be vigilant for possible fungal infections with your corneal transplant patients. "They're chronically immunosuppressed, so their symptoms will be more severe and their ability to respond to pathogens will be decreased." A fungus may find it easier to gain a foothold in the cornea of an immunosuppressed patient.



Figure 4. A case of *Candida* keratitis showing a nearly perforated cornea with a large necrotic area.

Sophie Deng, MD, PhD

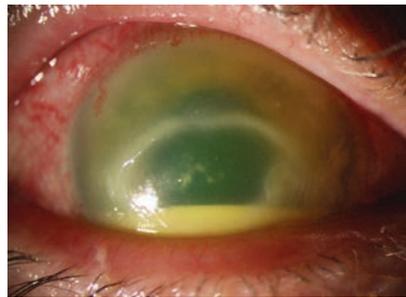


Figure 5. A case of severe *Acanthamoeba* keratitis with ring infiltrate, a large epithelial defect and hypopyon. On initial presentation, *Acanthamoeba* may be misdiagnosed as herpes, causing a delay in treatment and leading to a worse outcome.

Sophie Deng, MD, PhD

Antibiotic Resistance

Dr. Deng says that antibiotic resistance is concerning, particularly in a tertiary care environment. If your patient isn't responding to the treatment you've prescribed, checking the sensitivity report can point you toward other treatment options. "In general, you shouldn't base your treatment solely on the sensitivity," Dr. Deng cautions. "If the patient is responding to treatment, despite the report saying the sensitivity is intermediate or even resistant to the antibiotic that's been started, you don't have to change the medications. The patient administers drops very frequently, as often as hourly during the first days, so the amount of medication locally is much greater than the antibody level they test the sensitivity against.

"But if the patient isn't responding,"

she continues, "then I'd go by the sensitivity report. For example, an organism may be resistant to ciprofloxacin but sensitive to moxifloxacin, so I'd switch the patient to moxifloxacin and perhaps add another agent to target Gram-positives or Gram-negatives, depending on the patient's clinical course.

"Close monitoring of the infection is crucial at the beginning," she continues. "Because we are the main tertiary eye center in the area, we often see the most severe cases, where the central visual axis is affected and refractory to initial treatment by the referring ophthalmologist. We usually start fortified vancomycin and tobramycin/gentamicin if microbial infection is suspected."

Occasionally, the lack of response to treatment may be due to an incorrect or incomplete diagnosis. "If you need to reevaluate the causative agent—perhaps it's a fungal infection as well as a bacterial infection—you'll have to re-culture as well," says Dr. Deng. This can prove challenging, since a partially-treated ulcer may have a very low yield of microorganisms for analysis and prior treatment may skew results.

Corneal Biopsy

"Sometimes despite our best efforts, some corneal ulcers remain recalcitrant," Dr. Farid says. "In these cases we may move on to a corneal biopsy." A corneal biopsy may be necessary when there's no response from the organisms that grew on the first culture, or a poor response. In these cases, a biopsy of the deeper corneal tissues may reveal the elusive organism.

"Depending on where the infiltrate is, we may use a very small trephine punch that's about 3 mm," she explains. "We trephinate partially into the infiltrate and get a lamellar section of the diseased cornea to send for pathology. The risk here is perforation, so we have to be cautious and make sure we're not removing so much of the cornea as to cause a perforation."



Marian Farid, MD

Figure 6. If you notice a hypopyon in the anterior chamber after treating a bacterial keratitis ulcer, this is likely just a part of the inflammatory sequelae from killing bacteria, and not endophthalmitis, say.

Therapeutic Transplants

“In very severe cases when the cornea isn’t healing appropriately or the ulcer is very visually significant, we may move on to a therapeutic corneal transplant, where we’ll remove the entire infection, depending on the size and location of the infiltrate,” Dr. Farid says. “Here, patient history is important. If they’re immunocompromised or have rheumatologic disorders that would make them poor healers, these conditions would need to be assessed. Some patients will need systemic therapy as well. Fungal ulcers that are very deep may also require oral antifungals.

“We may also consider a therapeutic transplant if the eye is starting to grow blood vessels in from the periphery, because we know a corneal transplant is likely in the future anyway,” Dr. Farid continues. “Doing that therapeutic transplant before the patient gets a lot of peripheral neovascularization in the cornea can make the long-term chances of survival of the transplanted tissue better. That said, you also want to have the infection as well-treated as possible before heading for a transplant. There’s a sweet spot for the therapeutic transplant.”

Hypopyon or Endophthalmitis?

If you’ve given a patient the appro-

priate antibiotic for a garden variety *Pseudomonas* bacterial ulcer, and one or two days later, that patient returns with a hypopyon, Dr. Colby says don’t panic (Figure 6). “The white cell layer in the front of the eye doesn’t mean the infection has gone into the eye—it’s part of the inflammatory sequelae from killing the bacteria,” she explains. “This finding often generates an urgent referral to a cornea specialist, but it’s not endophthalmitis.”

“The way to distinguish endophthalmitis from a pure hypopyon in anterior chamber is through a B-scan to see whether there’s any vitreous opacity,” Dr. Deng explains. “The caveat, though, is that when the patient has such severe inflammation in the front of the eye, there’s often some spill-over inflammation—not necessarily infection—into the posterior pole. If there’s high suspicion for endophthalmitis—for example, if the patient has had cataract surgery and the patient presented with hypopyon before the corneal ulcer presented—then you would strongly consider endophthalmitis as one of the etiologies of the hypopyon. But if the patient presents with a bacterial corneal ulcer first and this leads to a hypopyon, then the chance of this eye having endophthalmitis as a presenting symptom is less likely.”

Endophthalmitis must remain on your radar for a fungal ulcer, however. Dr. Deng points out that fungi tend to penetrate deeply into the cornea, even into the anterior chamber. “This could lead to endophthalmitis,” she says. “If there is any concern of endophthalmitis, we always have our retina colleagues involved.” **REVIEW**

None of the doctors has financial disclosures related to any of the products mentioned.

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2. Leck A. Taking a corneal scrape and making a diagnosis. *Community Eye Health* 2009;22:71:42-3.

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Cross-linking 2020: Closer to the Holy Grail

Christopher Kent, Senior Editor

Epi-on cross-linking may soon be a reality. In the meantime, possible new approaches continue to appear.

Whenever a major new approach to treating a condition arrives on the scene, it goes through a period of evolution during which the process is refined and variations are suggested and tried. Corneal collagen cross-linking, primarily used as a way to address keratoconus and corneal ectasia, is currently in the midst of that process.

The biggest evolutionary shift taking place today is the move from procedures that require removal of the epithelium to ones that don't. However, other variations are being tried as well. Those include using cross-linking to cause refractive change; using cross-linking in combination with other procedures to increase the benefits experienced by the patient; miniaturizing the delivery system; triggering the cross-linking reaction chemically without UV light; and getting cross-linking to happen using oral riboflavin and sunlight.

Here, ophthalmologists and researchers share their work with each of these, provide updates on the current system approved by the FDA and discuss the status of other related ideas that are on the table.

Avedro/Glaukos: Epi-off & On

Currently, the only cross-linking

system approved by the U.S. Food and Drug Administration is Glaukos' iLink procedure (formerly known as Avedro's corneal collagen cross-linking procedure. Avedro was recently purchased by Glaukos.) The iLink system includes two proprietary riboflavin formulations, Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) and Photrexa (riboflavin 5'-phosphate ophthalmic solution, a hypo-osmolar formula that can be used if a thin cornea needs to be swollen), plus a UV light source. "This system has been available since 2016, and it's now well-accepted by cornea specialists and clinicians," notes Rajesh K. Rajpal, MD, a clinical professor at George Washington University Medical Center and chief medical officer for Johnson & Johnson Vision (formerly CMO for Avedro).

"Our primary goal has always been to get patients better access to the procedure," he says. "It took some time to accomplish, but the vast majority of insurers now cover it, and that's been accompanied by a significant increase in its use. The transition from Avedro to Glaukos actually helped, because Glaukos has been able to provide even more supporting research, as well as providing financing options for purchasers and reimbursement support, which have made

it easier for physicians to offer the cross-linking procedure and easier for patients to access it.”

Not surprisingly, the company is working hard to bring an epi-on system to market. “Leaving the epithelium on has obvious potential advantages in terms of safety, patient comfort and recovery time,” Dr. Rajpal says. “This could be especially beneficial for patients who need to minimize time away from school or work or whatever activities they may be doing.” He notes that the protocol under investigation also takes less time to perform. “It’s approximately a 30-minute treatment instead of a one-hour treatment,” he says. “The current iLink procedure requires 30 minutes of soak time and 30 minutes of light. The procedure under investigation is closer to 20 and 10 minutes, respectively, while the treatment goal remains the same.”

Dr. Rajpal says that the clinical Phase III studies of this epi-on cross-linking system have completed enrollment in the United States. “If the data meets the endpoint, the next step is submission to the FDA, with the potential for approval anticipated as early as 2022.”

Epi-on: Another Approach

Roy S. Rubinfeld, MD, MA, a clinical associate professor at Georgetown University Medical Center and medical director at Re:Vision in Rockville, Maryland, and Fairfax, Virginia, has devoted extensive time to developing an effective epi-on cross-linking system. He says the current proprietary version of the epi-on system that he began developing years ago, now called EpiSmart (owned by CXL Ophthalmics, based in Encinitas, California), is preparing to enter the final stage of FDA clinical trials.

Dr. Rubinfeld describes how the EpiSmart system overcomes the traditional obstacles to epi-on cross-link-



A keratoconus patient undergoes the iLink epi-off cross-linking procedure.

ing. “The first challenge is getting the riboflavin through the epithelium,” he explains. “Our proprietary riboflavin formula has been shown to rapidly, consistently and homogeneously penetrate intact epithelium and achieve corneal-stromal levels that allow excellent cross-linking.¹ The second thing that’s different is our delivery system for the riboflavin. Many techniques have been tried that involve disrupting the epithelium via abrasion to make it more permeable, or driving the riboflavin through with the use of something like iontophoresis. Our system applies the riboflavin using patented non-abrasive, disposable, sponge-based delivery devices that are gentle on the corneal epithelium, easy-to-use and sterile.

“The third unique part of the system is the third-generation UV light delivery device,” he says. “It delivers the UV light in a patented pulse cycle that allows oxygen to rediffuse into the cornea during the procedure. Without adequate oxygen, the cross-linking reaction can create toxic reactive oxygen species like peroxides, with side effects like haze, cell death, scarring (which coincidentally causes corneal flattening) and corneal thinning. These innovations are additive and synergistic, and each one is critical.”

Dr. Rubinfeld points out one other significant advantage of the system. “Traditional cross-linking procedures are done one eye at a time,” he says. “That causes the patient a solid week

of discomfort, and it takes many weeks for vision to return to preop levels. Then, after three months you start over and do the second eye. Our UV light source is designed for bilateral, simultaneous application, when indicated. By that evening or the following morning the patient’s vision is back to preop levels. The need to use opioids or bandage contact lenses is rare, as patients have just a few hours of typically mild to moderate discomfort.”

Evidence for Epi-on

Dr. Rubinfeld says that data published in the peer-reviewed literature has shown the EpiSmart system to be effective. “For example,” he says, “one publication describes 592 eyes treated with this system, 48 of which were pediatric eyes, which we know usually progress relatively quickly. In that paper, no eyes progressed after the treatment.² Some have dismissed these data because we didn’t include a placebo cohort or require documented proof of progression to participate in the study. However, we believe that waiting for patients to lose vision before treating a known degenerative eye disease is archaic, much like waiting to treat glaucoma until some of the visual field has been lost. Furthermore, the risk-benefit ratio with epi-on is unique. The fact that none of the 592 eyes progressed speaks for itself.”

Parag A. Majmudar, MD, an associate professor of ophthalmology at Rush University Medical Center in Chicago and president and chief medical officer at Chicago Cornea Consultants, agrees. (He participated in the trials of the EpiSmart system for the past 10 years, but switched to the FDA-approved epi-off system when the trial he was participating in was completed.) He notes that requiring proof of progression in some clinical trials is having an unintended side effect. “We’ve seen leading insurance companies deny treatment for young

patients who've started to lose vision simply because they don't have that proof," he says. "In addition, insurance companies give the flawed rationale that the patient sees well in contact lenses."

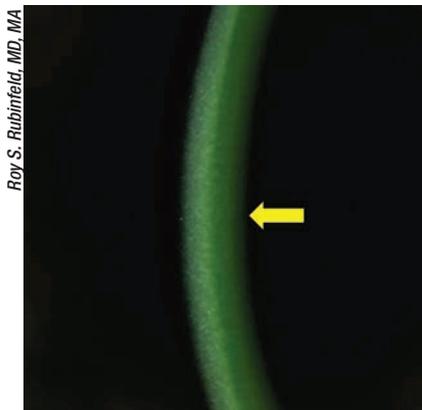
Dr. Majmudar notes that having to switch to an epi-off procedure made the advantages of epi-on very clear. "Having only done the epi-off protocol for a year I can't compare the long-term outcomes, but the number of patients having a much less pleasant experience and returning with corneal haze has been much greater. In the previous nine years I didn't see a single case of postop haze in more than 2,500 epi-on procedures."

Dr. Majmudar says that his personal experience with the epi-on system has been very positive. "Anecdotally, we've had a retreatment rate of about 1 to 2 percent, which is very comparable to the 2 to 3 percent within the first five years that's been reported in the worldwide literature using the Dresden protocol," he says. "We've had very high success rates and virtually no progression leading to the need for corneal transplantation during the entire nine years, which is, again, comparable to the Dresden protocol results. On top of that, we've had much better patient experiences." Dr. Majmudar suspects that the challenging patient experience is one reason some surgeons haven't been eager to offer epi-on cross-linking.

Dr. Rubinfeld says the EpiSmart system has now completed a Phase II trial and the company is moving toward Phase III.

CXL as a Refractive Treatment

Because the process of cross-linking tends to cause a small refractive change, the possibility of using an epi-on procedure for that express purpose has been under consideration for a number of years. A formalized version of that idea, known as photore-



A high-magnification, white-light slit lamp photograph of an eye treated with the EpiSmart proprietary riboflavin formula, designed to penetrate the corneal epithelium without disrupting or damaging it. After 15 minutes, the stroma is thoroughly and homogeneously loaded with more than enough riboflavin to allow effective cross-linking.

fractive intrastromal cross-linking, or PIXL, is now undergoing testing by Glaukos. "Multicenter Phase II trials of PIXL are being conducted outside the United States," notes Dr. Rajpal. "Those trials are designed to further refine treatment algorithms, evaluate outcomes and help the company determine the appropriate clinical and regulatory pathway in the United States. No specific timeline for that has been released."

Dr. Rajpal says the one target application anticipated for PIXL will be treating early presbyopia in patients who have fairly good distance vision. "This potential application makes sense in a patient with early presbyopia who is essentially emmetropic," he explains. "In that situation, your goal is to make the nondominant eye myopic, giving the patient monovision." (He notes that PRK and LASIK are rarely used to treat very low refractive errors because of the risk/reward balance.)

One of the issues that's been raised with using a procedure such as PIXL to effect refractive change is the difficulty of achieving a precise level of

change. "I don't think this can give you the level of refractive precision you can get with PRK or LASIK, because it's not removing tissue," Dr. Rajpal acknowledges. "Instead, we're changing the corneal shape, so it's inevitably going to be less predictable. But I don't think precision is the objective in this situation. When we're treating presbyopia, even if the patient gets some degree of improvement—perhaps intermediate vision instead of near vision—there's still a significant clinical benefit. In fact, in this situation patients are less critical about what the level of improvement is, as long as we're improving their ability to see up close—to see their phones or tablets or computers. Patients understand that presbyopia is progressive, so eventually they'll need another solution, but in the meantime, this could make a difference.

"Of course," he adds, "all of this will depend on the findings in the clinical trials."

Combination Procedures

Dr. Rubinfeld believes combining cross-linking with other procedures such as PRK (off-label) may be very helpful in cases of keratoconus. "There's been a lot of interest in combining treatments so that you not only stop progression but improve vision," he says. "For example, doing some sort of topography-guided PRK that removes limited tissue, and then cross-linking a few weeks later to lock in the effect, is very promising. This could markedly improve the lives of patients whose disease was not caught early."

"There are several techniques for combining cross-linking with a customized, partial-refraction ablation," notes A. John Kanellopoulos, MD, a clinical professor of ophthalmology at NYU Medical School in New York City and medical director of the Laservision.gr Institute in Athens, Greece. "I'm proud to report that

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Reference: 1. Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(19):2005-2015.

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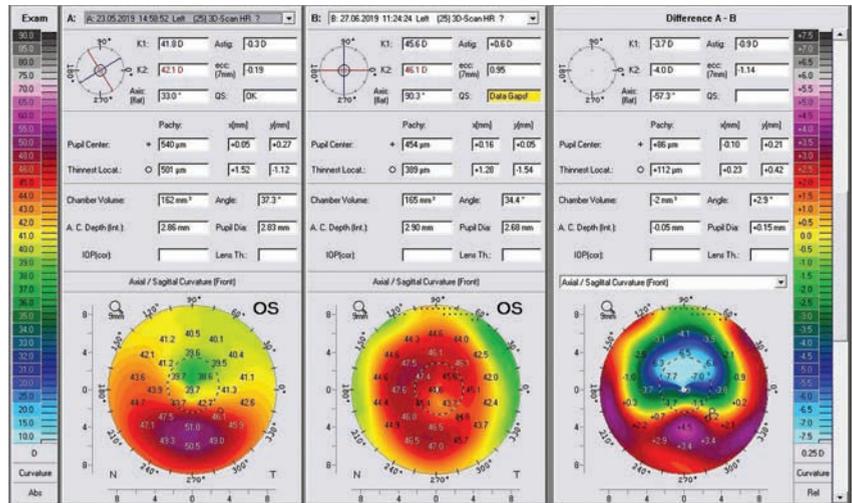
over the past few years my colleague Gregory Pamel, MD, and I have been able to combine topography-guided partial-refraction ablation with higher-fluence cross-linking in our New York City office, as well as in our Athens clinic. Our data, which mirror our European experience over the past 15 years, are currently under review for publication.”

If procedures are combined, there’s some debate about the order and timing of the procedures. “There have been cases of patients having cross-linking and PRK on the same day and ending up with a refractive surprise,” Dr. Majmudar points out. “If you do the procedures sequentially with some time in between, you might be able to better predict the outcome. Of course, this would be less of an issue if your goal is not to free the patient from wearing glasses, but simply to eliminate some of the higher-order corneal aberrations using topography-guided treatment.”

Dr. Rajpal says he believes that if procedures are done in combination, it’s logical to do the cross-linking first. “That way, you’ll know how much change has been induced by the cross-linking,” he notes. “If you do them at the same time and then the cornea changes because of the cross-linking, your refractive outcome may not be as predictable. Of course, this will come down to physician discretion.”

An On-eye System

One revolutionary new approach to performing cross-linking has been developed by Roy S. Chuck, MD, PhD, the Paul Henkind Chairman in the Department of Ophthalmology and Visual Sciences at Albert Einstein College of Medicine, Montefiore Medical Center in New York City, working with David Acker, a medical device entrepreneur, and Patrick Lopath, a biomedical engineer. They’ve found a way to miniaturize the UV light de-



Cross-linking can be combined with other procedures to improve a patient’s vision beyond what cross-linking can accomplish. Above: The left eye of a 26-year-old male with keratoconus, treated with partial-refraction topo-guided PRK combined with higher-fluence cross-linking using the Athens Protocol, demonstrates the efficacy and accuracy of this approach. Left: preoperative corneal tomography; middle: postop; right: difference map.

livery system so that it can be placed directly on the eye, a system they’re calling the CXLens. This miniaturization, in turn, makes it possible to monitor changes in the cornea in real time during the procedure.

“Several years ago I became interested in the idea of finding a way to make the cross-linking process easier for everyone by turning all of the cross-linking equipment into a wearable technology,” Dr. Chuck explains. “Instead of the UV light source being in an overhead lamp, our team put it inside a scleral contact lens—designed with help from colleague Deborah S. Jacobs, MD—which rides above the cornea, resting on the sclera. (See *picture*, p. 40.) This allows the patient to be ambulatory during the procedure.

“One of the benefits of this approach is that there’s no need to use an eye tracking system to ensure correct irradiation,” he continues. “Some cross-linking systems use an eye tracker that only notes when the eye turns away, shutting off the light in response. With our system, if the eye moves, the contact lens moves with it. Also, there’s no speculum holding the eye open; in

fact, the patient can close his or her eyes over the device. As a result, it’s more comfortable.”

Dr. Chuck and his colleagues realized they could add another key piece of technology to make this system even more useful. “We’ve embedded a tiny ultrasound probe into the apex of the lens,” Dr. Chuck explains. “This allows us to track the amount of corneal stiffening taking place in real time. This could be useful if you’re treating keratoconus, but it’s critical if you’re using corneal cross-linking to alter the patient’s refraction. When you can track the amount of corneal stiffening, you can directly correlate that with refractive change and modulate the treatment accordingly.” (Dr. Chuck was an early proponent of the possibility of using cross-linking to cause a refractive change.³)

“Knowing exactly how much change you’re causing has been an issue with every refractive treatment,” he notes. “Even with PRK and LASIK, in the early days no one knew how much energy to use to get the desired refractive change. It wasn’t until we had a lot of population data that nomograms



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were developed. Real-time monitoring is even more important when using cross-linking to generate refractive change, since this involves tissue remodeling rather than tissue ablation.”

As with every cross-linking system, two key issues tied to effectiveness are getting the riboflavin into the tissue and making sure sufficient oxygen is present for the reaction to occur in the desired way. Given the CXLens’ radically different treatment setup, Dr. Chuck explains how they’ve addressed these two issues.

“The way surgeons get the riboflavin into the tissue in a standard procedure has several drawbacks, such as the need for a nurse to put drops in the patient’s eye every few minutes,” he notes. “So, the first thing we did was to take a scleral lens—separate from the treatment lens—and use it as a reservoir. We put our riboflavin solution into the lens, place it onto the eye and then leave. When the tissue is sufficiently saturated, we switch to the treatment lens.

“Second, we’ve been developing our own formulation of riboflavin that can get past the epithelium without damaging it,” he continues. “For the pilot trials we had to use a currently available off-the-shelf trans-epithelial solution. These formulations aren’t ideal, as they use preservatives to disrupt the epithelium enough to allow passage of the riboflavin. The riboflavin formulation we’re developing opens up the channels between the epithelial cells without damaging them. It’s a technology invented by John Tomich, PhD, a biochemistry professor at Kansas State University; renowned ophthalmic researcher Henry Edelhauser, PhD, also spent time working on it near the end of his life. We acquired it from Kansas State University and are working with Dr. Tomich to perfect it. Once applied, our solution keeps those channels open for 90 minutes, letting the riboflavin pass through the epithelium. After that, the epithelium returns to its



Roy S. Chuck, MD, PhD

The CXLens system places the UV light source inside a scleral contact lens that sits on the eye, eliminating the equipment that would normally hover over the patient. It will also contain an ultrasound probe that can monitor corneal stiffening in real time, allowing controlled treatment for purposes such as inducing a specific amount of refractive change.

normal state.”

The other hurdle to overcome is making sure the cornea has plenty of oxygen during the procedure. “The contact lens does allow oxygen to pass through, but that’s not sufficient,” says Dr. Chuck. “We’ve developed a patient-protected method to use a special fluid as a very efficient carrier of oxygen; divers and intensive-care units in hospitals sometimes use a variation on this to help compensate for oxygen deprivation. We fill the space between the lens and the cornea with this fluid and it keeps the cornea oxygenated without the need to blow air across it.”

Dr. Chuck says they were able to complete a proof-of-concept trial involving 10 patients with advanced keratoconus in late 2019. “Fortunately, we were able to complete the three- and six-month follow-ups before COVID became an issue,” he says. “While we didn’t use our riboflavin formulation in this trial, the clinical results were very good. Now we’re in discussions with the FDA about taking this to the next stage, which will involve treating keratoconus and doing refractive cross-linking trials.”

Cross-linking Via an Eye Drop

One of the latest potential ap-

proaches to addressing keratoconus bypasses the use of riboflavin and UV light altogether. A twice-daily eye drop called IVMED-80, being developed by iVeena Delivery Systems in Salt Lake City, appears to be able to stop the progression of keratoconus (according to current data going out six months). The idea for this approach came from Bala Ambati, MD, president of the Pacific Clear Vision Institute in Eugene, Oregon, and a research professor at the University of Oregon. (Dr. Ambati is also the president and co-founder of iVeena.)

“As a cornea specialist I’m well aware of the challenges of epi-off corneal cross-linking,” Dr. Ambati explains. “In the course of my research as a clinician scientist I noted that lysyl oxidase, a natural enzyme in the cornea, mediates cross-linking. In fact, a deficiency of lysyl oxidase has been associated with keratoconus in multiple studies, which makes sense given the inadequate existing cross-linking found in these patients.⁴⁻⁹ One particularly nice study from Rohit Shetty, MD, examined the lenticles from patients who underwent the SMILE procedure and later developed keratoconus; the lenticles from those patients had below-normal levels of lysyl oxidase.¹⁰

“That got me thinking: If lysyl oxidase deficiency is a problem, how do we restore it to normal levels?” he continues. “Further research revealed that copper is a key element in lysyl oxidase activity, and that it, too, is reduced in keratoconic corneas. So, when we started iVeena in 2015, the first question we asked was: How can we increase lysyl oxidase to promote physiologic cross-linking in corneal tissue? The first obvious avenue to try was an eye drop containing copper. In one of our early experiments we tried a proprietary solution on corneal cells taken from healthy human corneas, or from keratoconus patients who’d undergone a corneal transplant. The

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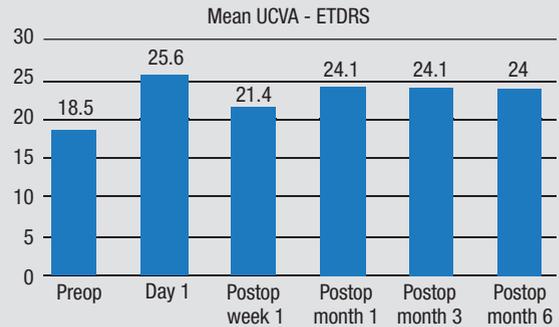
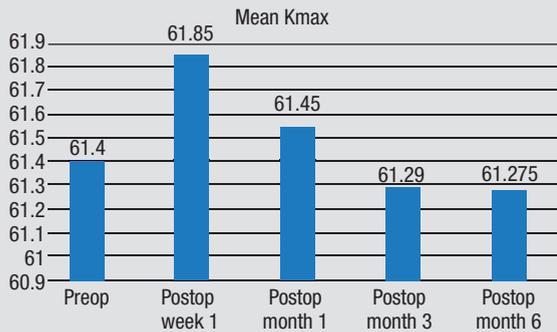
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Using a prototype of the CXLens contact-lens-based system for on-eye cross-linking, researchers conducted a prospective, non-masked, non-randomized clinical trial in eight eyes of eight patients with advanced keratoconus. Kmax values improved in 62.5 percent, remained stable in 25 percent and worsened in 12.5 percent of eyes. UCVA improved in 87.5 percent of eyes. BCVA was either stable or improved in 75 percent of eyes.¹³

solution did indeed increase lysyl oxidase activity in the cells.

“Next, we tested the IVMED-80 solution in rabbits and found that it increased cross-linking in the living rabbit eye,” he says. “Then we tried using the eye drops in the rabbit eyes twice a day for about seven weeks, and the corneas exhibited about 1.7 D of flattening. Most importantly, the drops were well-tolerated. There was no inflammation, no redness, no opacity and no damage to any of the rabbit ocular tissues. We also looked for copper accumulation in the plasma or liver or kidneys and found none.”

Dr. Ambati says they next moved on to a Phase I/IIa clinical study in patients. “We started the study in March, 2019 in Mexico, enrolling a series of 33 patients with keratoconus,” he says. “The study concluded this summer. One-third of the patients received placebo; one-third received the IVMED-80 drop for about six weeks, and another third received the drop for 16 weeks. We followed everybody for six months. By structuring the study this way we were able to evaluate the impact of the duration of therapy, as well as what would happen after stopping therapy.

“The overall results were excellent,” he continues. “At six months the pa-

tients who received the drug for 16 weeks had a K-max that was 2.3 D flatter than placebo. The patients who received the drug for six weeks got a little bit better but then returned to baseline by the end of the six months. Most importantly, there were no treatment-related adverse events. There was no inflammation, pain or redness induced by the drug. It was very well tolerated, with no issues.

“Based on the averages, it looks like there was no regression in the 16-week group after stopping the drug,” he adds. “We’ll see if that was true for every patient when we analyze each patient individually. I think duration of treatment may end up depending on age and severity of progression.”

Dr. Ambati says his team will be completing the statistical analysis of the trial data over the next couple of months. “We should have a final report before the end of the year,” he says. “The next step is to proceed with the U.S. clinical development pathway, and we’re already working with the FDA. Hopefully we can start the Phase III studies late next year.”

Treating With Oral Riboflavin

In the past few years, John S. Jarstad, MD, FAAO, a professor of

clinical ophthalmology at the Morsani School of Medicine, University of South Florida-Tampa, has been working with a very low-tech, inexpensive approach to cross-linking he stumbled onto a few years ago that’s showing promise in clinical testing. In this protocol, patients simply take an oral riboflavin supplement every day and walk vigorously (to increase oxygenation) toward the sun at midday for 15 minutes each day without wearing sunglasses or UV-blocking contact lenses. Remarkably, he says this protocol seems to produce results equal to those seen with the more high-tech, costly cross-linking treatments. The trade-off is that it takes several months to be effective.

Dr. Jarstad came up with the idea when trying to help a desperate patient who couldn’t afford the high-tech options, which weren’t covered by her insurance. In the clinical trial he conducted to test this approach (NCT03095235 at the NIH trial website) every patient taking 400 mg/day of riboflavin and following the walking protocol—except for one patient who never removed his UV-blocking contact lenses—achieved corneal flattening (average: 1.2 D), with keratoconus progression halted. A control group taking 100 mg/day also stabilized

but saw less corneal flattening. Effects have been observed within three months, but the best results have generally been measured at six months.

A commonly raised concern is possible toxicity from the oral riboflavin. Dr. Jarstad reports that no adverse effects have been observed in any patients, noting that one colleague reported that a patient took 1,500 mg per day with no side effects (and an even greater flattening). He also notes that he hasn't found any reports of complications associated with high-dose riboflavin in the literature.

Recently, Dr. Jarstad has noted that this approach also seems to be helping patients who have previously undergone radial keratotomy. "One patient in our study had eight-incision RK in 2008 and suffered from fluctuating vision for many years," he says. "When I first saw her in May of 2016, as she began our study, she had post-RK ectasia with K readings of 33.9 by 35.6 D in her right eye and 35.9 by 37 D in her left eye. Her best-corrected vision measured 20/40 in the right eye and 20/30 in the left eye. After participating in the protocol her keratometry readings stabilized, and they've been stable since then. In June of this year, her visual acuity measured 20/20 without correction and her keratometry readings showed less than 0.75 D of astigmatism in each eye."

The low cost and positive results are generating interest in other countries. Leonardo Torquetti, MD, PhD, an ophthalmologist and cornea specialist from Brazil who treats many keratoconus patients, has been trying this protocol on keratoconus patients who are at risk of progression. He reports that none of those patients have progressed since he began this treatment. He reports that other doctors in Brazil are trying the protocol as well.

Another remarkable finding reported by Dr. Jarstad has been that his study of this protocol also appears to confirm reports in the literature that

Treatment Pearls

A. John Kanellopoulos, MD, a clinical professor of ophthalmology at NYU Medical School in New York City and medical director of the Laservision.gr Institute in Athens, Greece, offers these suggestions to achieve better results when performing cross-linking:

- **Emphasize that your patient must avoid eye-rubbing.** Dr. Kanellopoulos points out that avoiding eye-rubbing is critical when the eye is recovering from an epi-off procedure. "This needs to be continuously reinforced to patients and their families," he says.

- **Rely on corneal imaging when screening for keratoconus or ectasia, not visual acuity.** "Visual acuity decline, which is often the first thing motivating patients to seek ophthalmic help, is not a good metric for ectasia," he points out. "We've all seen advanced keratoconic patients in their teen years with 20/20 uncorrected visual acuity. So, it's imperative to screen these patients for keratoconus and ectasia using corneal imaging."

- **Treat keratoconus as an inheritable disease.** Dr. Kanellopoulos explains that his clinics have found an almost 100 percent familial predisposition in keratoconus patients. "Over the past two years, when we image the parents of known keratoconus patients using corneal imaging with Scheimpflug technology and/or anterior segment OCT to measure cornea thickness and map the epithelium, we've found keratoconus or significant keratoconic suspicion in at least one parent in almost 100 percent of the patients," he says.

- **Take courses in early diagnosis of keratoconus.** Dr. Kanellopoulos says his team frequently gives courses in the early diagnosis of keratoconus and the use of different cross-linking devices and techniques, as well as their work combining cross-linking with different types of surface ablation, at the major ophthalmology meetings.

— CK

oral riboflavin can provide major relief from migraine headaches and ophthalmic migraine. "We first noticed this when patients in our study with a history of migraines reported that their migraines had stopped," he says. "Following this discovery we began using this approach to treat patients with ophthalmic and classic migraine symptoms, including patients with intractable migraine. So far, in 79 out of 80 patients treated with 100 mg of riboflavin capsules taken by mouth per day—increasing by 100 mg each week up to 400 mg/day for those not responsive to 100 mg/day—we've seen a cure of their migraine variants."

Other Options and Issues

As corneal cross-linking continues to evolve, different methods for accomplishing it continue to appear, while some past protocols are falling by the wayside.

- **Altering parameters to speed**

the process. "The top cross-linking photochemists that I've talked to consider this idea to be ill-advised," says Dr. Rubinfeld. "This premise is based on the Bunsen-Roscoe law of reciprocity, which suggests that the results of 5 minutes of 50 mW/cm² UVA exposure has the same effect as 50 minutes of 5 mW/cm². This law applies in the photography darkroom, but not in the biological world. Also, the rate-limiting factor is oxygen, not UV light. The majority of the peer-reviewed literature suggests that accelerated cross-linking is inferior to standard treatment. You may cut the length of the procedure by a few minutes, but the outcomes generally aren't as good."

- **Loading the riboflavin into a stromal pocket.** Getting the riboflavin into the stromal tissue via a femtosecond-laser-created cornea pocket (similar to that created for the SMILE procedure) is an idea that was pioneered by Dr. Kanellopoulos' group about 10 years ago, as a way to avoid

having to remove the epithelium. However, the positive results being seen with other less-invasive epi-on approaches has prevented this idea from becoming widely used. “The stromal pocket approach is currently mostly an investigative tool,” Dr. Kanellopoulos says.

• **Approaches that compensate for thin corneas.** The idea that UV light might damage the endothelium if the cornea is too thin—i.e., less than 400 μm thick—was proposed by Gregor Wollensak, MD, in 2004.¹¹ This has led to several protocols that can be used to ensure that corneas are at least that thick prior to cross-linking. However, the validity of that requirement is now being challenged.

“Subsequent studies of the epithelium have demonstrated that 400 μm is not a magic number below which cross-linking will be a disaster,” says Dr. Rubinfeld. “In fact, Mooren et al conducted a study in which they took a human cornea, put some riboflavin in and turned it upside down; then they directly irradiated the endothelium with continuous UVA of 18 mW/cm^2 .¹² While acknowledging the limitations of an *ex vivo* study, the authors conclude from their findings that human corneal endothelial cells are more resistant to UVA irradiation in the presence of riboflavin than was previously estimated based on animal experiments. This suggests that many of the protocols that have been developed to ensure that cross-linked corneas are at least 400 μm thick may be unnecessary, if the corneas are treated with cross-linking systems that balance the cross-linking reaction.

“In fact,” he adds, “our epi-on technology has safely treated a large number of very thin corneas without swelling them or using a contact lens.”

• **Customizing the procedure based on corneal thickness.** Dr. Rajpal believes that customizing treatment based on individual corneal characteristics is a worthwhile goal.

“Ultimately I think we’ll find ways to do that as we gather more data and understand patient outcomes better,” he says. “The idea of doing less treatment or modifying where the treatment is done based on the thickness of the cornea or steepness of the cornea may be achievable once there are adequate clinical data available.”

Dr. Kanellopoulos notes that his group has done a lot of work with customized cross-linking since 2013, using the Avedro Mosaic device. “It makes sense as a way to employ cross-linking to cause refractive changes in the cornea in a more controlled and predictable fashion,” he says. “I think it holds great promise for the future.”

Dr. Rubinfeld, however, is skeptical. “This is an interesting concept, but to what end?” he asks. “The primary use for this procedure is to improve or maintain vision and prevent further deterioration in cases of keratoconus and ectasia. I don’t think this type of customization would make much difference.”

• **Using iontophoresis to drive the riboflavin through the epithelium.**

Dr. Rubinfeld notes that this approach isn’t widely used. “It’s extremely painful,” he says. “We started using it in 2010 or 2011 but stopped using it by 2012. In recent years, when I lectured in Europe I’d ask if anyone had used iontophoresis and most hands would go up. Then I’d ask if anyone was still using it, and pretty much everybody dropped their hands.”

Dr. Kanellopoulos agrees that there’s little evidence of its current use. “It seems that its initial advantage in epi-on cross-linking has been bypassed by other topical agents that can achieve the same result,” he says.

Good Medicine in Any Form

No matter which cross-linking approach (or approaches) prevail, Dr. Kanellopoulos believes that cross-linking will have a major impact on how

corneal problems such as ectasia and keratoconus are addressed. “If clinicians around the world become astute in diagnosing these conditions and offering treatment early,” he says, “we should be able to eliminate the need for cornea transplantation.” **REVIEW**

Dr. Rajpal is CMO at Johnson & Johnson Vision and a consultant for Glaukos. Dr. Rubinfeld is on the board of CXLO, is a named inventor on all of the U.S. and European patents for its cross-linking system and is managing member of CurveRight LLC. Dr. Majmudar is a consultant for Alcon and an investor in the CXLO EpiSmart epi-on system. Dr. Kanellopoulos is a consultant for Avedro and Alcon. Dr. Chuck is co-founder and co-owner of TECLens, developer of the CXLens. Dr. Ambati is president and co-founder of iVeena and has an equity interest in the company. Dr. Jarstad reports no relevant financial ties.

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We would like to invite you to review the upcoming 3rd-Year Ophthalmology Resident Programs and Wet Lab for January and March 2021 in Fort Worth, Texas. The programs offer a unique educational opportunity for your current third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide your residents with a state-of-the-art didactic and wet lab experience. The programs also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

Best regards,
Kendall Donaldson, MD, Yousuf Khalifa, MD, Mitchell Weikert, MD, MS

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(Friday - Saturday)

Course Director:
Yousuf Khalifa, MD

January 29-30, 2021
(Friday - Saturday)

Course Director:
Kendall Donaldson, MD

March 5-6, 2021
(Friday - Saturday)

Course Director:
Mitchell Weikert, MD, MS

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For more information: Visit the registration site above
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Dealing With the Unhappy IOL Patient

Sean McKinney, Senior Editor

How to manage surface disease, residual refractive errors, off-target corrections, troubling visual disturbances and more.

As you know, ensuring patient happiness after cataract surgery can be difficult at times, requiring you to explore the use of lens exchanges, piggyback lenses, refractive surgery with lasers, capsulotomies, management of ocular disease and other interventions to put a smile on the faces of frowning patients.

“Satisfying unhappy patients is always a priority, especially when it comes to premium IOLs, because patient expectations are so much higher than they otherwise would be,” says Brandon Ayres, MD, assistant surgeon at Wills Eye Hospital and an instructor at Jefferson Medical College, Thomas Jefferson University in Philadelphia.

“These patients are paying out of pocket, and they expect to pay for performance,” he continues. “Many times, you get that performance but sometimes you don’t. So at times it can be sort of a tricky pathway to follow. With any cataract surgery, we have to be prepared to use a number of options—or combination of options—to achieve our goals.”

Through the years, surgeons have crafted personal protocols for trouble-shooting and meeting the challenges of these cases. In this report, leading surgeons share insights on their approaches.

Your Start Time

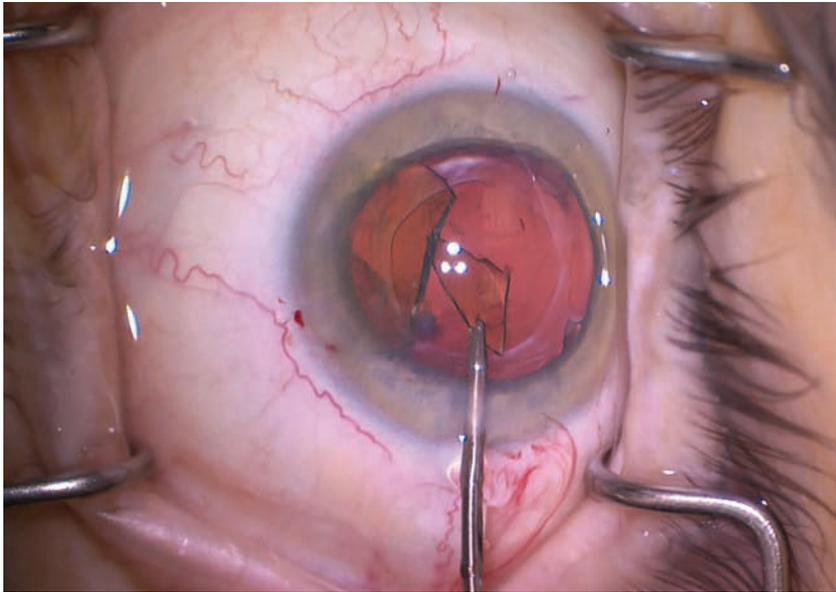
Although effective responses to unwanted outcomes are critical to your surgical plan, planning for the worst by doing your best before surgery is equally important, according to Mark Kontos, MD, senior partner at Empire Eye Physicians, which has offices in eastern Washington and northern Idaho.

“The best way to deal with postop issues is to not have to deal with them because you’ve taken the time to understand what patients want before surgery,” he says. “Understanding their expectations can significantly increase the likelihood of achieving happiness.”

Below are key questions that Dr. Kontos uses to guide his preop conversations with patients:

- Do you want to be free of glasses?
- Do you care if you’ll still need glasses after surgery?
- Do you want clear distance vision without the need for glasses?
- Do you want to read without glasses but don’t care about wearing glasses to see clearly at a distance?

A reality check is also critical. “Are the patients’ expectations based only on what they’ve been told by family and friends who’ve had cataract



Brandon Ayres, MD

Figures 1-A and 1-B. Fragments of an inadequate IOL are carefully removed (left) to make way for a replacement IOL (right) during this lens exchange.

surgery?” asks Dr. Kontos. “Do their descriptions of the surgery and their anticipated results match the procedures you’re planning plus their best potential outcomes? The more you probe, the better you’ll be able to educate them on what’s possible.

“For example, you might not be able to offer the laser cataract surgery that your patient’s friend underwent. Or you might need to tell a patient with macular degeneration who wants a presbyopia-correcting lens that this won’t be a good combination.”

On the technical side, Dr. Ayres tries to avoid what he calls “a patient selection error.”

He emphasizes the essential need for you to use proper communication with the patient, keeping in mind that today’s ever-advancing IOL technology requires increased precision in offering patients the right refractive solution.

“Near vision expectations vary with these new IOLs,” he notes. “We need to consider the differences among expanded-depth-of-field, multifocal and accommodating IOLs. A careful slit lamp exam as well as a good understanding of the psychology of

the patient are critical.”

Two-step Protocol

Despite the clearest preop counseling you can provide, some patients will always be unhappy after the procedure, points out Preeya K. Gupta, MD, a corneal specialist at the Duke Eye Center. Dr. Gupta, another firm believer in deep listening as a first step in partnering with preop patients, puts dissatisfied patients’ postop concerns in two categories:

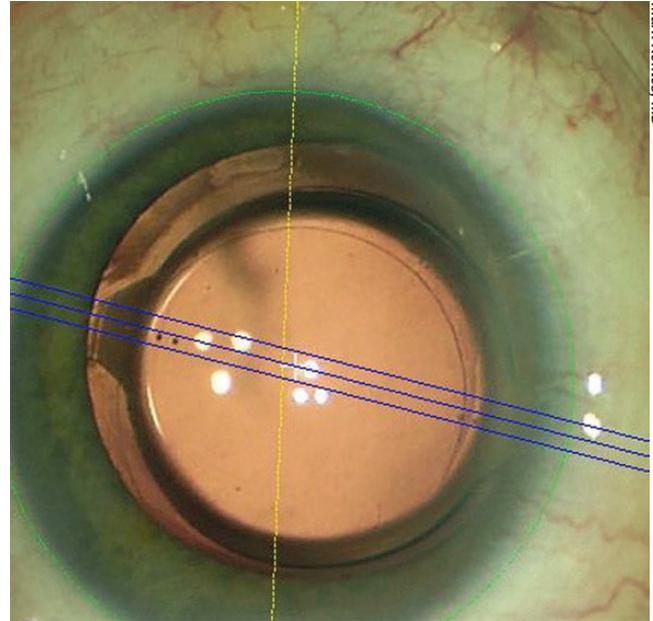
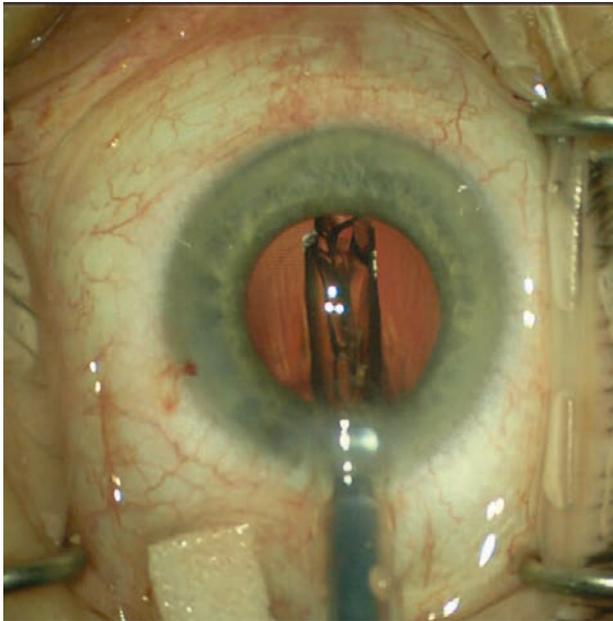
1. early postop period, within the first month; and
2. beyond the early postop period.

“I spend a lot of time with unhappy patients to identify what’s bothering them after surgery,” she says. “Is it sensation? Pain? Irritation? Blurred vision? And so forth. I think that most clinicians who effectively address postop unhappiness are comfortable hearing complaints during the first few weeks after surgery. The most common issues are blurry vision, irritation or some other form of discomfort. These symptoms account for about 90 percent of what patients complain about the most early on.”

The rest of the issues belong in what Dr. Gupta calls the “the large other” category—those sometimes-challenging, sometimes-simple, usually-infrequent and typically-not-serious postop issues. “Some patients might be affected by negative dysphotopsias, which can develop early on after the implantation of any type of intraocular lens,” says Dr. Gupta. (See “Update on Dysphotopsias” on page 50.) “Some patients may perceive halos or glare—far more commonly after multifocal IOLs have been implanted.”

Dr. Gupta’s practice provides a handout that explains these symptoms, describing them as typically short-lived and experienced by many other postop patients. “The handout also offers trouble-shooting advice,” explains Dr. Gupta. “This resource saves a lot of phone calls to the office. It goes a long way in terms of helping to set realistic expectations.”

Typically, after 30 days, pain and inflammation have subsided, she notes, adding that the structural integrity of the eye is fairly consistent and stable in 99 percent of postop patients at this point. “Many problems that persist relate to ocular



Figures 2-A and 2-B. This patient pays for the implantation of a toric IOL (left) then returns to the OR with blurry vision two weeks later so that a Zeiss Callisto system can be used to reposition her misaligned lens (right).

surface disease, which is very common among the limited number of patients who are still having trouble,” she says. “Pre-existing dry eye is typically the most difficult postop challenge we face. Many cataract patients are older, obviously, and many of them have ocular surface disease that hasn’t been diagnosed preoperatively. They may have been asymptomatic and become symptomatic because of surgery. That’s one large area of potential concern. And certainly this can cause blurred vision.”

From All Directions

Dr. Ayres says he sees a disproportionate number of unhappy post-cataract patients. “I’m often sent patients who, for whatever reason, are either not seeing well or aren’t happy with their vision, whether it’s loss of contrast or unwanted images, such as halos, negative dysphotopsias, etc. I try my hardest not to create my own unhappy patients. But of course if you’re putting lenses in, you’re going to have a patient at some point who

isn’t happy with a lens.”

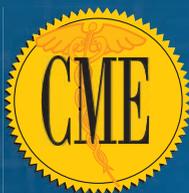
His goal is to problem-solve thoroughly and do lens exchanges only when it’s absolutely necessary. “In any study, when you read of unhappy patients, especially those with premium IOLs, residual refractive errors and ocular surface disease are two of the leading causes,”¹ he says. “If you can address these issues, you can make unhappy patients happy. If you’re off-target with their IOLs—say a toric is misaligned, you can go back and realign the toric. Or it may require you to rely on the manifest refraction to shed light on the problem. That’s where the ‘magic eraser’ of the excimer laser comes in. You can do a refractive procedure, whether it’s LASIK or PRK, and meet patient expectations.”

Frequently, Dr. Ayres discovers an opportunity on the corneal surface to turn a case around. “When I look closely, I might see a little anterior membrane dystrophy along with a bit of undiagnosed dry eye,” he says. “I’ll usually put these patients on a prescription anti-inflammatory, such as

cyclosporine (Restasis) or lifitegrast (Xiidra). He also relies on preservative-free tears, topical steroids, punctal occlusion and autologous serum, as needed, and he aggressively treats co-existing conditions, such as dry eye and blepharitis. “With enough time and treatment, you can get these patients to be at least satisfied enough with their vision to opt to keep the lens and not undergo a lens exchange,” he says.

How long should you wait for a positive turn of events? It depends on the source of the underlying problem, according to Dr. Ayres. “If we see a nodule or anterior basement membrane dystrophy that requires a superficial keratectomy to remove, an effective solution can sometimes require six to eight weeks,” he says. “Those are actually the easier cases, because you have a very defined problem and solution.”

More traditional dry-eye disease can be more difficult. “The treatment of the ocular surface is quite challenging,” says Dr. Ayres. “This disease is very easy to diagnose and



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Update on Dysphotopsias

Persistent positive and negative dysphotopsias after cataract surgery continue to cause significant patient dissatisfaction, but new IOL designs and alternative surgical strategies may mitigate these side effects of modern IOL implantation, according to a literature review by experts on the topic published in the August edition of *Ophthalmology*.¹ Samuel Masket, MD, and Nicole R. Fram, MD, who based their review on 39 relevant articles obtained through a PubMed search, considered factors involved in both forms of these visual disturbances, which are often transient and which frequently affect patients only in certain lighting conditions or positions.²

Positive dysphotopsias. These effects, perceived by patients as glare, arcs, streaks, rings and halos, are primarily related to oblique light-rays that strike the square (truncated) edges of IOLs and reflect onto the retinal surface. Besides the edge design of today's IOLs, IOL optical design, a high index of refraction and surface reflectivity play a role in causing positive dysphotopsias. Fewer cases are associated with IOLs modified with a round anterior edge and a square posterior edge. However, no round-edged foldable IOLs are currently available in the United States. Based on their surgical experience, Drs. Masket and Fram observe that changing the optic material to a lower index of refraction has improved symptoms in the majority of cases.

Negative dysphotopsias. Negative dysphotopsias are associated invariably with well-centered "in-the-bag" IOLs. These multifactorial effects, manifesting to patients as shadows, dark spots or crescents typically perceived in the temporal visual field, are less understood than positive dysphotopsias, in part because of a lack of agreement between clinical and laboratory findings. Researchers using ray tracing optical modeling suggest that temporally incident light rays reach the nasal retina and pass anteriorly back up through the IOL. Some of the light is refracted posteriorly by the IOL, resulting in the temporal shadow. Other implicating factors include nasal anterior capsule override, haptic orientation, large angle kappa and high hyperopia. Persistent negative dysphotopsias have been successfully treated or reduced with reverse (anterior) optic capture, sulcus IOL placement, piggyback IOLs and Nd:YAG capsulectomy along the nasal aspect of the anterior capsule overlying the lens optic, according to Drs. Masket and Fram.

1. Masket S, Fram N. Pseudophakic dysphotopsia: A review of incidence, etiology and treatment of positive and negative dysphotopsias. *Ophthalmology* 2020; Aug 12. [Epub ahead of print].

2. Radmall BR, Floyd A, Oakley Z, et al. Refractive index and its impact on pseudophakic dysphotopsia. *Clin Ophthalmol* 2015; 9:1353–1358.

not so easy to treat—and to treat well. So those patients might take two to four months before they turn around. And sometimes, treatment needs to include an office procedure, such as a LipiFlow or some other kind of meibomian gland/blepharitis therapy."

Planning for the Unexpected

Of course, refractive surprises always remain a potential problem in the cataract surgery arena. At Empire Eye Physicians, Dr. Kontos responds calmly to surprises with a

consistent approach. "If a patient is hyperopic to a significant and bothersome degree, our general feeling is to go ahead and do a lens exchange," he says. "If the patient requires a minor myopic correction, we're more inclined to use the excimer laser. We can do low corrections on patients pretty easily. We'll often look at those patients and do a postop LASIK or PRK procedure to manage an issue without having to return to the OR to address it intraocularly."

Dr. Kontos believes a lens exchange is appropriate if the myopic postop correction is more than 2 D

off-target. "If we have myopia under 2 D, whether we do a lens exchange depends on how the patient feels," he explains. "Sometimes, patients in this category will think the wrong lens are in their eyes. And if they have that concept in their minds, exchanging the lens may be the only thing that will make them feel better. For hyperopic patients, I might consider a lens exchange under 1 D, but certainly more than 1 D. Quality of vision is just going to be better with a lens exchange for these patients."

Dr. Kontos says the use of today's advanced technologies, such as the IOL Master 700 (Zeiss), has reduced the likelihood of a significant myopic surprise. "But if it were to occur, say in a post-RK patient, or some post-LASIK patient for whom we get a big surprise, then we would do a lens exchange without hesitation," he says.

Like Dr. Ayres, Dr. Kontos returns his patient to the OR if he confirms an axis rotation issue in a toric IOL. "We find these issues are generally quick and easy to manage," he notes. "We'll take them back to the OR and realign the toric lens. Or, if need be, we'll exchange that lens."

In most cases, however, Dr. Kontos and his colleagues try to avoid a repeat trip to the OR for the same eye. "It's pretty hard to take a patient back for a second time for the same eye," he reflects. "Most patients will feel as if their surgery didn't go as planned, obviously. If we can just say, 'Hey, we can provide a minor laser treatment to do a little touch up on you, and we'll get you right where we want you to be, it seems more like a simple matter that's more acceptable to patients, like a contingency plan we've already developed.'"

Dr. Ayres says he and his colleagues usually succeed in avoiding unwanted second surgeries. But inevitably? "You'll have the patients who—no matter what you do—are just not happy with the quality of their vi-

sion,” he says. “They’ve tried glasses, maybe even undergone refractive surgery, been on Restasis or Xiidra or any other fill-in-the-blank treatment for dry eye, and they’re just not happy with the quality of their vision. Often, these patients find it difficult to see with good contrast. These are the patients for whom we’ll do a lens exchange. Every so often, they will have already undergone a YAG capsulotomy to treat a little bit of a PCO. So we have to be ready to do a vitrectomy. Usually, though, these patients will do very well.”

After exchanging an IOL, Dr. Ayres recommends waiting to evaluate the result of the procedure before performing an exchange on the fellow eye. “Very often, for unhappy bilateral multifocal implant patients, when we exchange a lens in one eye, we find the exchange seems to reduce dysphotopsia to the extent that they’re happy enough and we opt to leave the second eye alone,” he says. “They realize they have some near vision from that second eye, helping them function as if they have monovision. And to me, that’s a happy patient.”

Residual Refractive Error

Like other surgeons, Dr. Gupta says residual refractive error, potentially developing for a number of reasons, can be a significant source of postop unhappiness among the patients. “There can be errors in biometry,” says Dr. Gupta. “Of course, we do all the tests, but how the lens actually fits into the eye and functions isn’t always predictable. That’s when the art of cataract surgery comes into play.”

She outlines what she calls the “nuts and bolts” of teasing out issues affecting an unhappy postop cataract patient. “My rule of thumb: I like to check the patient at regular intervals to make sure the refractive error is



Brandon Ayres, MD

Figure 3. A superficial keratectomy is used to treat anterior basement membrane dystrophy in this postop patient, allowing him to eventually achieve optimal vision without the need for an IOL exchange.

stable,” she says. “For a relatively small refractive error, such as 1 D to 2 D, generally speaking, I find laser vision correction, achieved with PRK or LASIK, can be an excellent treatment. For patients with larger refractive errors, an IOL exchange any time within the first three to six months postop is reasonable. An IOL exchange is also a reasonable option for patients with multifocal lenses who really can’t tolerate the halos, for whatever reason.”

In some cases, Dr. Gupta says the unhappy patients have aberrated corneas from subclinical pathology that wasn’t recognized at the time of surgery. “I go step by step through a detailed examination of the patient’s anatomy, often using topography. I also prefer a dilated exam to make sure we haven’t missed any retinal pathology, such as macular degeneration, epiretinal membrane or macular edema.”

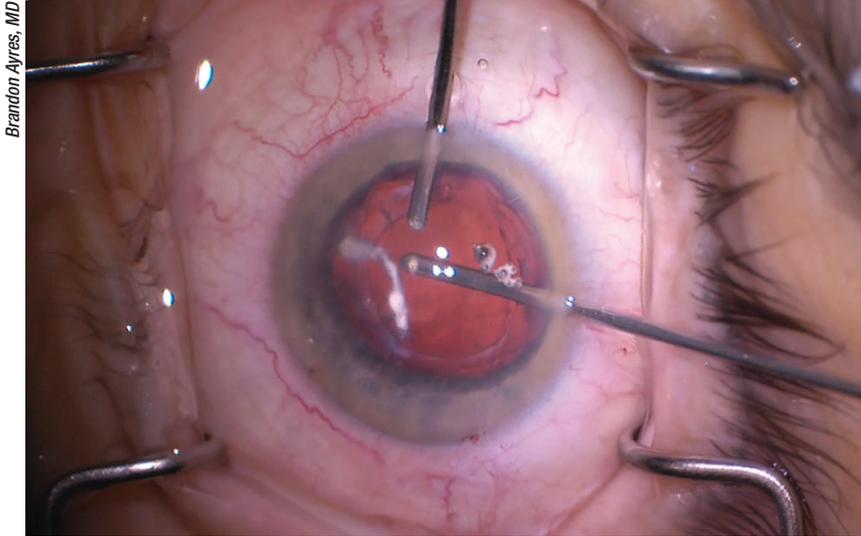
In addition, she looks for abnormalities in the cornea. While surface-related pathology is generally easier to recognize and treat, she notes: “I sometimes feel a need to refer a patient for specialty contact lens fitting. By then, we typically will have identified aberrations, combining to-

pography with tomography, to document information on the shape of the cornea.

“If a patient gets fitted with hard contact lenses and their vision improves, the fitting takes on a diagnostic function because it’s safe to assume that the aberrations were indeed the cause of the visual complaint,” she continues. “If the patient can tolerate the contact lenses, this approach can also become therapeutic. Many of these patients can wear hard contact lenses, which are able to reshape the aberrated cornea, permitting light to enter the eye when the light is bent in a regular pattern.”

However, not all patients with aberrations find themselves with better vision from hard contact lenses. “These cases are harder for us to solve because there really isn’t anything to go back to surgically,” says Dr. Gupta. “We don’t have a technology that can necessarily selectively treat corneal aberrations.”

When surgeons discuss the ways to keep postop cataract patients happy, the idea of implanting IOLs on top of IOLs—the “piggyback” approach—doesn’t come up as much as in years past. Dr. Gupta says piggyback IOLs are “certainly an option, but one that



Brandon Ayres, MD

Figure 4. Following a YAG capsulotomy, this patient, undergoing an IOL exchange, requires an anterior vitrectomy before implantation of the new IOL.

isn't used very often." She adds: "Piggyback lenses may be used for patients who are very myopic or very hyperopic. In those cases, you may have no additional IOL powers that will allow them to benefit from a simple IOL exchange. So these are the patients who most often benefit from piggyback lenses."

Premium Challenges

As Dr. Ayres mentioned, surgeons put themselves most at risk of creating unhappy patients when implanting premium IOLs, raising the expectations of patients who may demand more performance than is possible from a lens. "I'm very open and up-front with my patients about premium lenses," says Dr. Ayres. "I'll say that the more modern generation of trifocal implants have been performing much better, with a lower complication rate and dissatisfaction rate, than the prior IOLs. The newer technology has really made it easier for us to meet the highest of patient expectations."

Besides relying on advanced technology, his additional strategy for keeping this cohort of high-spending

and high-maintenance patients satisfied is his direct approach. "I always involve my patients in decisions and tell them what's going on with their surgery," he explains. "I tell them that what they're paying for isn't necessarily a better lens. It's decreased dependence on reading glasses. We're not talking about putting in an inferior lens if they opt to not go with the trifocal IOL and instead just choose another quality lens from several good options. Then, the issue is how close the measurements are and how close to plano we can get them, although none of my patients would want to end up at zero."

After implanting the first premium IOL for a patient, Dr. Ayres schedules a follow-up visit one week later to make sure his patient is happy with his or her vision, mindful that he's typically planning for both eyes. "We need to confirm that the patient wants to continue with this newer technology for the second IOL implant," he says. "If the patient's not happy, then we deal with the issue right then and there. That's when we might decide to use that second surgical date, already scheduled, to do a lens exchange, if one is needed.

If our biometry was off, or we just have to slow our plan down and treat a dry-eye problem—whatever the issue—right then is when we plan what we're going to do. Or we take care of whatever needs to be addressed to satisfy the patient. We like to have the patients help determine what's going to happen next, so they don't feel forced into something they don't want to do."

And if the patient is unforgiving? Drs. Ayres recommends you consider the following explanations, without making it seem that you've done something wrong:

- **Measuring the eye before surgery is not an exact science.** "Patients need to understand how difficult this can be and how we try to do our best on that first shot," says Dr. Ayres. "We don't always get precise measurements."

- **Implants only come in certain sizes, requiring surgeons to estimate the best fit for a patient's eyes.** "We only have 20-mm, 25-mm and 30-mm lenses," he explains. "The patient's measurement may actually be at 20.75. So we need to take a best-fit approach. Truth be told, with the benefits of neuroadaptation and other approaches, I usually have these patients worked out within six months. But I prefer to do a lens exchange if we're off by a significant amount. If the biometry is off, I can exchange even a premium lens without charging the patient." If you end up needing to replace an IOL, Dr. Ayres notes that you can bill under the diagnosis of dysphotopsia.

- **Laser vision correction is just part of the plan.** "It's always possible that you'll get to a point when laser vision correction is necessary," says Dr. Ayres. "I tell patients this during the first surgical visit, so they're not surprised if it becomes necessary. I assure them that if we need to use an approach that's safer or better for achieving best correc-

tion, then we can go with the laser, which I offer at cost. They understand I'm not trying to make more money on them. I'm just trying to ensure that we achieve the highest quality of vision possible."

When to Charge for More

Dr. Kontos says the decision on whether unhappy postop patients should be required to pay for procedures after the initial surgery depends on what he and his patient have agreed on before surgery. "If patients ask for clear distance vision and we're incorporating the femtosecond laser into their procedures to correct astigmatism, and we're doing some additional imaging and taking other steps to make sure we get them to plano, we consider the fact that these patients are already paying out of pocket for the surgery," he notes. "If we need to do any further work, then we don't charge those patients."

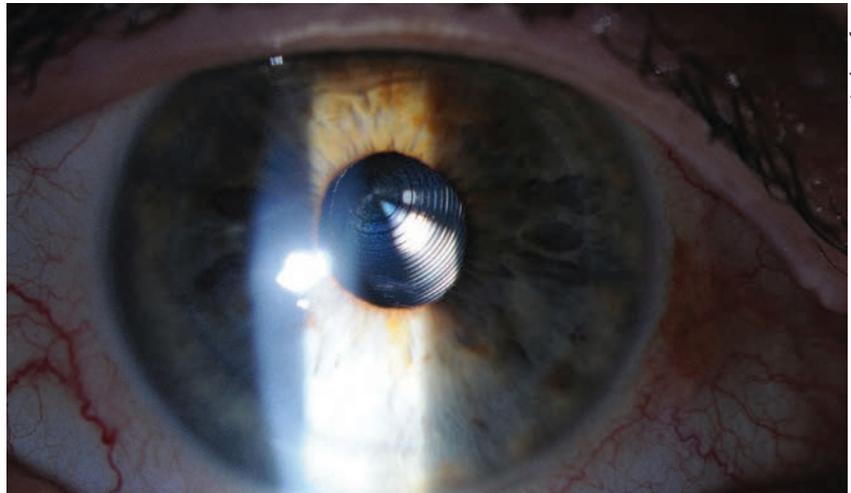
Dr. Kontos says the patients who come to his practice fall into three categories:

1. Those who plan to get only what insurance will cover and who want the surgeon to "do the best you can for me."

2. Those who want to see distance clearly and settle for reading glasses for near vision.

3. Those who want as much independence from their glasses as they can get, such as those who would pay extra for a multifocal or EDOF IOL.

"Patients will pick one of these options and we'll manage them accordingly," says Dr. Kontos. "One of the things that's hard is when a patient comes in after a friend has had surgery and the friend doesn't need to wear glasses for distance anymore. The friend might see great and was able to use only his health insurance to pay for the surgery, without incurring any expenses beyond the standard co-payment. Now my patient,



Preeya Gupta, MD

Figure 5. This patient's problem is no mystery. Her decentered IOL will need to be fixed as soon as possible.

the friend of the completely satisfied patient, wants the same treatment from me, but he has 1.5 D of cylinder. Unless I do something special to correct that, I'm just not going to satisfy the patient to the extent that his friend was satisfied. This is where that preop discussion becomes so important. If you don't educate the patient and agree on realistic goals, you're setting up a patient for unhappiness after surgery."

Dr. Ayres says his practice keeps its premium cataract surgery cost lower than other practices. "That's why we do laser vision correction at cost, if we need to do it," he adds. Other practices bundle that potential laser enhancement cost within the price of their premium cataract surgery. So that enhancement, if necessary, is offered free by those practices.

"Whether you charge or how much you charge for the laser also depends on whether you own the laser or if you have to use a laser center or if someone else is doing the laser treatment for you," he explains. "Because we try to be very accurate with the use of our biometry, we may only need to offer a refractive surgery enhancement for one in 20 patients. We don't want to bundle in the cost of a laser treatment that

won't be used for those 19 other patients. That wouldn't be fair."

Stand by Your Patient

From a clinician's standpoint, surgeons agree that your top priority when you have an unhappy cataract patient is to always stand by the patient's side. "At the very least, promise the patient that you're going to help work through the problem," says Dr. Gupta. "I think when patients get shuffled through the process or feel like someone isn't hearing them, that's when it becomes a less manageable situation. Most patients are reasonable and can understand that not everything can be the best at all times. But they still want to make sure that surgeons are doing their best to keep them at the top of mind." **REVIEW**

Dr. Ayres is a consultant for Alcon, Carl Zeiss Meditech and Microsurgical Technology. Dr. Kontos is a consultant for Zeiss, Sun, Allergan and J & J Vision. Dr. Gupta is a consultant for Alcon.

1. Gibbons A, Ali TK, Waren DP, Donaldson KE. Causes and correction of dissatisfaction after implantation of presbyopia-correcting intraocular lenses. *Clin Ophthalmol* 2016;11:10:1965-1970.

Tips for Success with Trifocal Lenses

Michelle Stephenson, Contributing Editor

Surgeons discuss the pros, cons and tips for implantation for a new breed of intraocular lens.

As many surgeons know, making patients happy with their premium intraocular lenses can be a challenge. It only gets harder when the premium lens is relatively new to the market and has a unique design. Though the PanOptix trifocal IOL (Alcon) offers the potential benefit of providing sharp vision at distance, intermediate and near, surgeons may still have questions regarding patient selection and what kind of results to expect with the lens. Here, experts share their insights on the new IOL.

The Lens's Design

The PanOptix is composed of foldable acrylic, and has a 6-mm optic. The optic diffractive structure is in the central 4.5-mm portion of the optic and divides the incoming light to create a +2.17 D intermediate and a +3.25 D near add power at the IOL plane (approximately +1.65 D and +2.35 D at the corneal plane).¹ The anterior surface is designed with negative spherical aberration.

The posterior surface of the toric PanOptix is marked with six indentations on the flatter meridian.

Where Trifocals Fit in the OR

Surgeons note that there are some

noticeable differences between trifocals and other multifocal lenses that use a bifocal approach. “[Bifocal multifocals] have a specific near point,” explains South Carolina surgeon and Alcon consultant, Kerry Solomon. “Depending on the add of the lens—there’s a +2.25, +2.75, +3.0, +3.25, and a +4 add, for example—there’s one specific point in space where things are clearest with a little bit of a range. The trifocal has two focal points, and they’re spaced out such that there’s very little drop-off between the focal points. A multifocal, for example, with a +3 add falls off at intermediate vision. A multifocal with a +1.5 add, or an extended-depth-of-focus lens with a +1.5 to +1.75 add falls off in the near. A trifocal, because it has more than one area of best focus, gives a larger range of vision.”

Though trifocal proponents say they appreciate the lenses’ range of vision, many use them as just one of the arrows in their quiver. Having both trifocal and EDOF lenses gives the surgeon more options for patients, according to Uday Devgan, MD, who is in practice in Los Angeles. “EDOF lenses like the Symphony (Johnson & Johnson Vision), which have diffractive rings, seem to function like a low-add bifocal diffractive IOL with reasonable intermediate and far vision,

but not quite enough near vision without spectacles,” he says. “The Vivivity EDOF from Alcon, which is already available in Canada, does not have diffractive rings on it, but instead is a newer type of EDOF lens that uses other optical methods to elongate the focal range to a degree.”

If you’re planning to get involved with the PanOptix trifocal lens, surgeons say to expect certain advantages and disadvantages. “The idea of EDOF IOLs having a single wide peak in the defocus curve, versus multiple peaks, does provide a degree of forgiveness when it comes to refractive targeting,” says Daniel Chang, MD, a Johnson & Johnson Vision consultant who practices in Bakersfield, California. “We’d all like outcomes with perfect distance, intermediate and near vision, but surgeons unfortunately miss the refractive target or leave residual astigmatism more often than we like to admit.

“When this happens, we’re shifting the defocus curve either to the right or to the left, so the distance peak doesn’t hit plano,” he continues. “If we have a broader peak and we miss the refractive target, we can still maintain good distance vision, albeit at the possible loss of near. In comparison, with bifocal/trifocal IOLs, the distance peak is going to get smaller, so it’s more critical to nail the refractive targets. From a usability standpoint, EDOF technology offers better refractive forgiveness than bifocal/trifocal IOLs. Additionally, since EDOF IOLs like the Symphony provide image quality that’s comparable to aspheric monofocals, common issues like missing the refractive target, posterior capsule opacification and dry eye can be better tolerated because of the superior image quality.”

He adds that he doesn’t intend to use the PanOptix, because of concerns about the AcrySof platform. “While I think trifocal IOLs can have a benefit, I have concerns about PanOptix

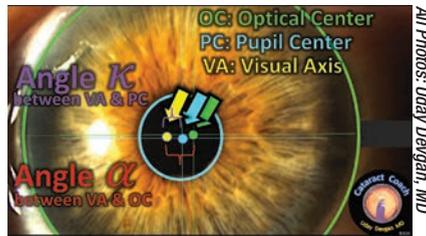


Figure 1. A patient with significant angle alpha and angle kappa, which means that the visual axis of the eye is not closely aligned with either the pupil center or the optical center of the eye. Surgeons say any IOL with diffractive rings will suffer from suboptimal performance in this situation, because surgeons will be unable to center the IOL in the visual axis and simultaneously align the diffractive rings with the pupil.

both from a material and from an optical properties standpoint,” he says. “The high-index AcrySof material has high reflectance, glistenings and poor chromatic aberration, which can lead to image-quality issues. It can also have frost along the edges, is prone to scratches during folding and implantation, and tends to pit more easily from YAG capsulotomies than other hydrophobic acrylic materials.”

However, Boston’s Bonnie An Henderson, MD, who consults for Alcon, believes that trifocal lenses are a valuable addition to the currently available IOLs. “No lens is perfect, but trifocal lenses deliver what they promise, which is near spectacle-independence,” she says. “Because the previous multifocal IOLs were bifocal lenses, they only provided uncorrected vision at two distances rather than three. The launch of trifocal IOLs has been a welcome addition to the presbyopia-correcting IOL armamentarium. Originally, I was concerned that a trifocal IOL would increase the risk of positive dysphotopsias. I have been pleasantly surprised that this hasn’t been the case. In fact, the trifocal IOLs have been well received by patients without an increase in the incidence of unwanted side effects.”

According to Dr. Solomon, the

secrets to success with trifocals are patient selection, good surgical planning in order to make sure you hit the refractive target, and patient education on the front end. “Let patients know about the night-vision issues so they’re not surprised,” he says. “And make them aware that, even with a good surgical plan that’s striving to hit the target refraction, there’s a 15- to 20-percent chance that you’ll need to do a secondary procedure like a PRK or LASIK touch-up, to get them where they need to be, and that’s expected. However, if you have a good, healthy eye, hit the target refraction and perform good patient selection, you should have terrific results and very happy patients.”

Patient Selection

According to Dr. Solomon, anyone with healthy eyes, including a healthy ocular surface, is a candidate for trifocal lenses. “I’ve also had good success using them post-refractive surgery,” he says.

He also adds that it’s important for patients to be told that the lens splits light. Because the lens has rings in its design, patients will notice rings and halos at night. “In the FDA studies, the vast majority of patients, 95 percent, found these to be very mild or moderate, tolerable, and not a distraction at all,” Dr. Solomon says. “Five percent of the patients rated the night vision issues as severe. However, even in that 5 percent, the majority didn’t want the lens removed because the rest of their vision was so good that they tolerated the night-vision issues. I reassure patients that the rings are supposed to be there. I show them an image of what the rings look like, and the vast majority of patients say that seems fine or that they’re already experiencing that with their cataract. I explain that it will look different after the cataract removal, but it shouldn’t be distracting to them. The

vast majority of patients have no issues, and the overwhelming majority, once they're implanted, do very well. Approximately a third of my patients don't notice the rings even though we know they're there; one-third of them notice them but say they get better with time—they don't, but the brain adapts; and one-third say they notice the rings to varying degrees but they don't limit their vision. In the rare instance that this does limit their vision, we can take the lens out and exchange it for something else."

It's important to have this conversation with every patient, because some people don't want even a small chance of compromised night vision, surgeons say, adding that this might be a niche to be filled by an EDOF lens like the Symphony or Vivify.

Also, patient expectations need to be managed, says Dr. Devgan. "There is no such thing as the fountain of youth for vision," he says. "Even with a trifocal, you're not going to see like a 25-year-old. With trifocal lenses, you still have the compromises of splitting the light, which is what gives you nighttime glare and halo, as well as decreased contrast. I ask my patients to choose between two sentences: (1) 'I want the very best quality of vision, the best night vision, the best contrast, and I will wear reading glasses,' or (2) 'I don't want to wear reading glasses and, to achieve that, I'll happily sacrifice some quality of vision, especially at night when I'll see some glare and halos.' Usually, with one of those sentences, I can tell whether a patient has the right mental attitude for the lens. If patients say they want perfect quality of vision, and they also don't want to wear reading glasses, then we simply don't have anything that will meet their expectations."

Surgical Planning

Surgeons say there are a couple of considerations when you intend to

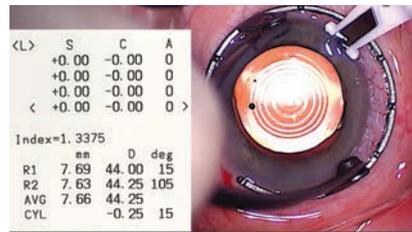


Figure 2. Trifocal IOLs work best when surgeons can achieve a plano outcome, including treating even small degrees of corneal astigmatism.

implant a trifocal lens.

"You should have an otherwise completely healthy eye," Dr. Devgan avers. "Any problem that exists in the eye tends to be magnified when you put in a light-splitting lens. These lenses are for completely normal eyes in which you as the surgeon can hit your refractive target, even treating small degrees of astigmatism to achieve a plano outcome. I also preoperatively check the angle alpha and angle kappa to see how well the pupil is lining up with the visual axis. During surgery, you're going to place this diffractive lens in the center of the pupil. If their visual axis is somehow off, they may not achieve good-quality vision." To help with the implantation of the toric version of the lens, Alcon offers a web-based calculator at <https://www.myalcon-toriccalc.com/>.

In terms of results, in the U.S. Food and Drug Administration study of the lens, half of the 127 PanOptix patients could see 20/20 at near binocularly, uncorrected, vs. just 0.9 percent of the monofocal IOL patients (total n=111). Ninety-two percent could see 20/25 or better at near vs. 9 percent of the monofocal patients. At intermediate distances, 73 percent of the trifocal patients could see 20/20 vs. 22.5 percent of the monofocal group, and 93.7 percent of the trifocal patients could see 20/25 or better compared to half of the monofocals. (Monofocal IOLs gave slightly better uncorrected distance vision in the study, with 78.4 percent of monofocal patients seeing

20/20 or better vs. 73.2 percent of the trifocal patients; and 94.6 percent of the monofocal group seeing 20/25 or better, compared to 92 percent of the PanOptix group.¹)

Starbursts, halos, and glare were the most frequently cited visual symptoms in the PanOptix group. For glare, 3.2 percent rated it as "severe," vs. 1.8 percent of the monofocal patients in the study. In terms of halos, 12.6 percent of the PanOptix patients described them as "severe," compared to only 0.9 percent of the monofocal patients. Finally, 16 percent of the PanOptix patients said their starbursts were "severe," vs. 1.8 percent of the monofocal patients.¹

When implanting premium lenses, Dr. Chang says that the surgeon has to strike a balance between image quality, range of vision and night-vision symptoms. "With both refractive and diffractive optics, the more range of vision that you provide, the more image quality you stand to lose," he says. "Unless you compensate for your range-of-vision increase with something like the correction of chromatic aberration, visual quality can suffer. From a night-vision standpoint, more near vision results in more off-axis light that can lead to dysphotopsias, such as glare, halos and starbursts. So, the reason the Crystalens or the ReSTOR 2.5 has minimal night vision symptoms is because they provide minimal near vision. The relationship isn't hard-and-fast, but the trend is tied to the optics." **REVIEW**

Dr. Chang is a consultant with Johnson & Johnson Vision, and he is an investigator for the IC8 IOL for Acufocus. Dr. Devgan was formerly a consultant for Alcon, AMO/Abbott and Bausch and Lomb. Drs. Solomon and Henderson are consultants for Alcon.

1. FDA Summary of Safety and Effectiveness Data, Alcon PanOptix. https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040020S087B.pdf. Accessed September 22, 2020.



I was only seeing light flashes early on, but light

FLASHES

when you've not seen anything for
so many years—it was wonderful

—Keith H, retinal prosthesis recipient

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Canaloplasty, GATT & Trypan Blue Venography

Combining these procedures can be therapeutic and may reveal important information about the status of the outflow system.

Gavin Docherty, MD, FRCSC, and Patrick Gooi, MD, FRCSC, Kelowna, British Columbia, and Calgary, Alberta, Canada

Ab interno canaloplasty and gonioscopy-assisted transluminal trabeculotomy, or GATT, have been in use for several years. Each has a track record of effective intraocular pressure lowering in many patients, but they aim at different targets; GATT addresses resistance at the trabecular meshwork by unroofing it, while canaloplasty addresses resistance at the trabecular meshwork, inside Schlemm's canal and in the collector channels through which aqueous exits the anterior chamber, by inflating Schlemm's canal from the inside with viscoelastic.

Recently, we've been combining these procedures, with a modification to the canaloplasty procedure that helps reveal the condition of the post-trabecular aqueous outflow system. In this article we'd like to explain the rationale behind our modified combination procedure and describe how it's performed, in the hope that this will inspire further investigation and advancement in this area.

Using Canaloplasty

Canaloplasty is a therapeutic pro-

cedure. Basically, it involves injecting viscoelastic into Schlemm's canal; the OVD also works its way through the collector channels and aqueous veins. This procedure is thought to increase outflow through a number of mechanisms: 1) creating microfenestrations in the trabecular meshwork, thereby reducing resistance at this level; 2) releasing intracanalicular adhesions and clearing debris within collapsed portions of the post-trabecular outflow system; and 3) opening physiologic valves that regulate outflow.

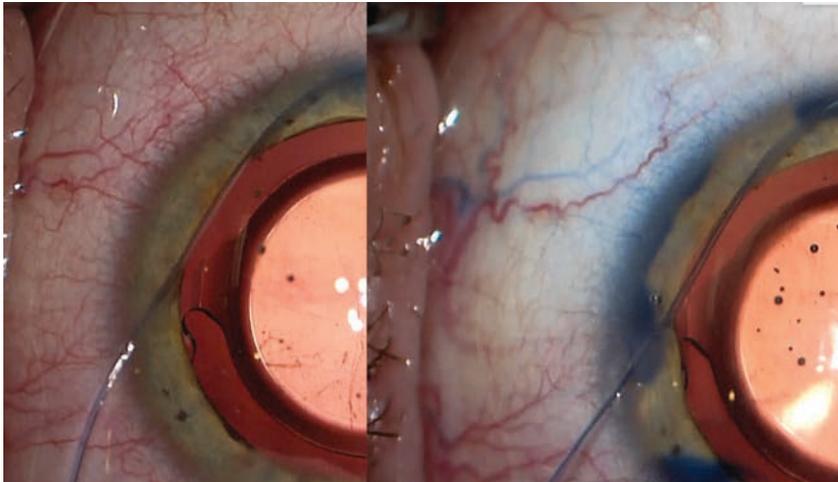
In the past, reduced outflow was thought to be the result of debris or atrophy blocking a simple, stationary filtering system, with the trabecular meshwork acting as the filter. Since then, Murray Johnstone, MD, has demonstrated that the outflow system

involves multiple one-way valves that help to move fluid from Schlemm's canal into the collector channels in a pulsatile manner, similar to the way lymphatic veins have been shown to work.¹ (This comparison has been supported by work done at the University of Toronto by Yeni Yucel, MD.²) Injecting viscoelastic during canaloplasty may permanently force open those valves, thus decreasing the resistance to flow through the pathway. Therefore, it's possible that this procedure is not just clearing away debris inside Schlemm's canal, but is actually making the outflow system more efficient.

There are two approaches to performing canaloplasty: *ab externo* and *ab interno*. (We prefer the latter.) *Ab externo* was the method initially described. In this version, the surgeon creates a partial-thickness scleral flap allowing the insertion of a catheter into Schlemm's canal. In the *ab interno* version, we enter the eye via a clear corneal incision and access Schlemm's canal through a small goniotomy. (Both versions of the canaloplasty rely on the Ellex's iTrack 250- μ m microcatheter, which



Trypan blue is added to a vial of viscoelastic to perform venography.



In trypan blue venography, after injecting a mixture of trypan blue and viscoelastic into Schlemm's canal, draining episcleral vessels and episcleral blanching are easily identified. Above: Before and after injecting the mixture.

incorporates a fiber optic light that allows the surgeon to visualize the progression of the catheter's tip during the 360-degree insertion.)

One significant advantage of *ab interno* canaloplasty is that we preserve the conjunctiva, which is important when managing glaucoma. As glaucoma surgeons, we're always planning our next move in case the current procedure doesn't work well enough. (Unfortunately, glaucoma patients tend to progress despite our best efforts.) Preserving conjunctiva and minimizing scarring increases the odds of success if we need to do a trabeculectomy or tube later on.

Trypan Blue Venography

During canaloplasty we pressurize Schlemm's canal with viscoelastic, and some of it is distributed through any functioning collector channels. We realized that this provides an opportunity to visualize the status of the post-trabecular outflow system; all that's required is to make the viscoelastic easier to see. That's easily accomplished by adding trypan blue to the viscoelastic before it's injected into the canal. Seeing where the viscoelastic is exiting into the collector

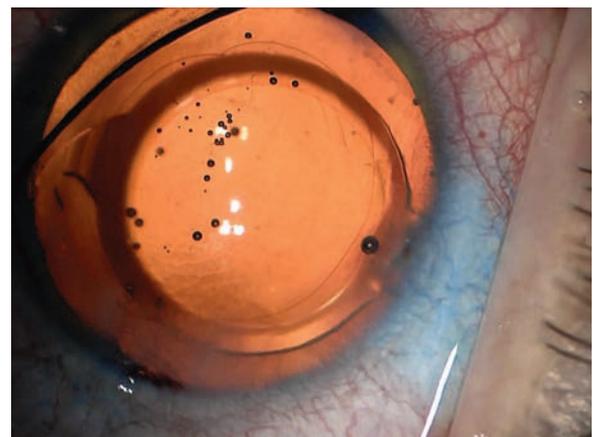
channels and outflow system (which may include lymphatics in addition to veins) can help us make treatment choices based on information we haven't previously had, while also helping to increase our understanding of the outflow system in general.

A related idea using balanced salt solution to look for what's called the "fluid wave sign" has previously been described. In this method, when the anterior chamber is hyperinflated with BSS, you see transient blanching of the aqueous veins, indicating a patent post-trabecular outflow system.³ In comparison, our method using trypan blue mixed into viscoelastic during canaloplasty makes it much easier to visualize the pattern, distribution and caliber of the aqueous veins. Furthermore, some surgeons have used fluorescein to observe outflow fluid movement,⁴ but using trypan blue eliminates the need for special equipment to observe it. We refer to our process as "trypan blue

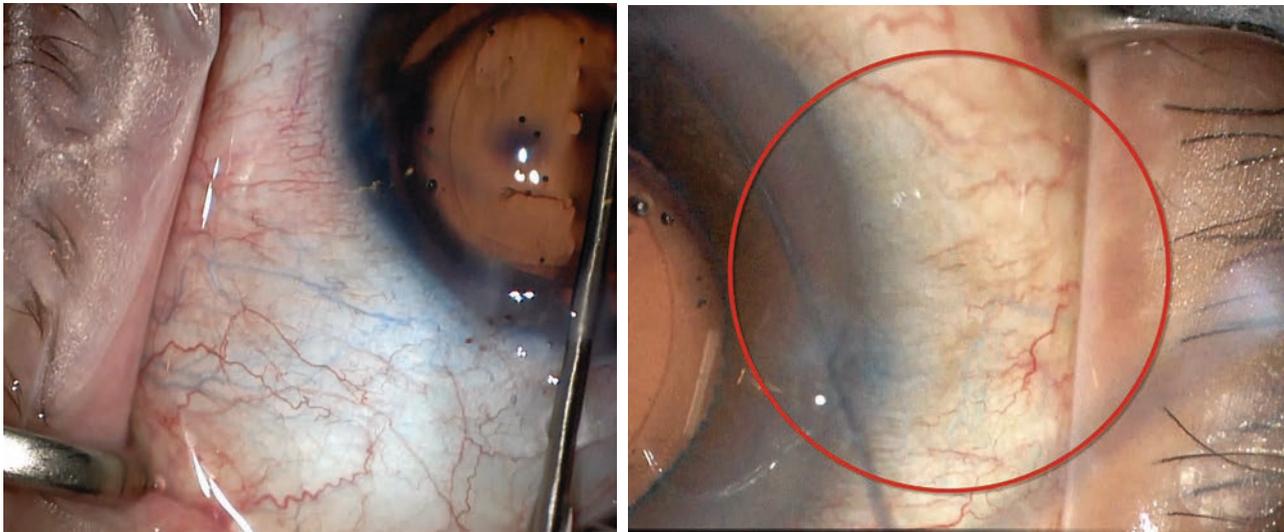
venography," even though the blue staining observed in some patients falls outside of the veins—which, again, suggests the presence of a lymphatic system in the sclera.

This modification of canaloplasty provides crucial information about the condition of the outflow system. If little or no outflow is seen—especially after the therapeutic effect of a canaloplasty has been applied—the outflow system may already be damaged beyond repair, and attempting to enhance the natural outflow system may not achieve the desired surgical result. In that situation, switching to an option that creates a nonphysiologic outflow system, such as a subconjunctival gel stent, trabeculectomy or tube shunt, might make more sense.

We've observed several different responses when trypan blue has been used in this manner. First, in some patients we see minimal-to-no trypan blue staining; these are the patients who would probably benefit more from going directly to a gel stent, tube or trabeculectomy. Second, some patients have a more sectoral or fine response, in which some areas show trypan blue staining in a limited fashion. A third group shows diffuse outflow, where we see multiple areas of vessel staining, which we feel is a favorable prognostic indicator.



After injecting the mix of trypan blue and viscoelastic, a "blue blush" seen between episcleral vessels may indicate intrascleral drainage of aqueous.



Left: After injecting the mix of trypan blue and viscoelastic, this eye demonstrates an extensive pattern of distinct episcleral vessels. Only a minimal “blue blush” between vessels is observed in this case. Right: This eye had developed advanced pseudoexfoliation glaucoma. It shows a less-intense venographic pattern. This may suggest the presence of an atrophic post-trabecular outflow system.

Finally, some patients show what we call a “blue blush,” where we see not just the vessels but diffuse staining within the sclera. This may indicate an intrascleral plexus that may consist of very small outflow vessels. Seeing a blue blush is probably a good sign in terms of being able to enhance the existing outflow mechanism. (Note: At this point we haven’t done enough cases to provide statistical support for an association between specific venographic patterns and different types of glaucoma.)

Performing the Procedure

To perform this procedure, we use a cohesive OVD—Healon. These OVD cartridges are compatible with the injector mechanism for the iTrack. We inject a 0.5-mL vial of trypan blue into the container using a 1-inch, 25-gauge needle. Then we use the shaft of the needle to mix the viscoelastic and trypan blue until the mixture is as homogenous as possible. We then insert the OVD/trypan cartridge into the iTrack apparatus. The iTrack has a mechanism for injecting the viscoelastic with clockwise turns; every turn releases about 250 µm of

material.

Next, we create a temporal incision, as well as a superior and/or inferior paracentesis (depending on which angle of approach we want to take), and insert the iTrack through the paracentesis. To achieve an *en face* view of angle structures, we tilt the patient’s head away from us and tilt the microscope about 35 degrees. We begin by filling the anterior chamber with a supercohesive OVD such as Healon 5 to create stability and prevent blood reflux from angle structures. Then, visualizing with a gonioscope, we create a small goniotomy in the trabecular meshwork using a 25-gauge needle; this acts as an entry site for the iTrack catheter. As we visualize the small goniotomy incision we’ve made in the trabecular meshwork, we insert the iTrack through it using micrograspers.

Once we’re confident that we’ve inserted the iTrack into Schlemm’s canal for two to three clock hours, we rotate the patient’s head as well as the microscope back into the primary position; this facilitates visualization of the iTrack’s fiber optic illumination and advancement through the canal. This position also

enables simultaneous viewing of the post-trabecular outflow system. We proceed to inject the viscoelastic and trypan blue mixture as we carefully advance the catheter and observe the subsequent venographic pattern around the illuminated tip.

Currently, we’re cannulating and viscodilating the complete 360 degrees to assess the post-trabecular outflow system. Traditionally, most patients have a higher density of collector channels in the inferonasal quadrant. Interestingly, we’re finding a number of patients that have a higher density of collector channels in the superior quadrants. We still have much to learn about how the various venography patterns affect surgical outcomes.

Why Add GATT?

About 90 percent of the time we follow our modified version of canaloplasty with a GATT procedure. In the GATT procedure, Schlemm’s canal is unroofed by pulling on the iTrack microcatheter used to perform the canaloplasty while it’s still inside Schlemm’s canal. (There are some contraindications to performing the

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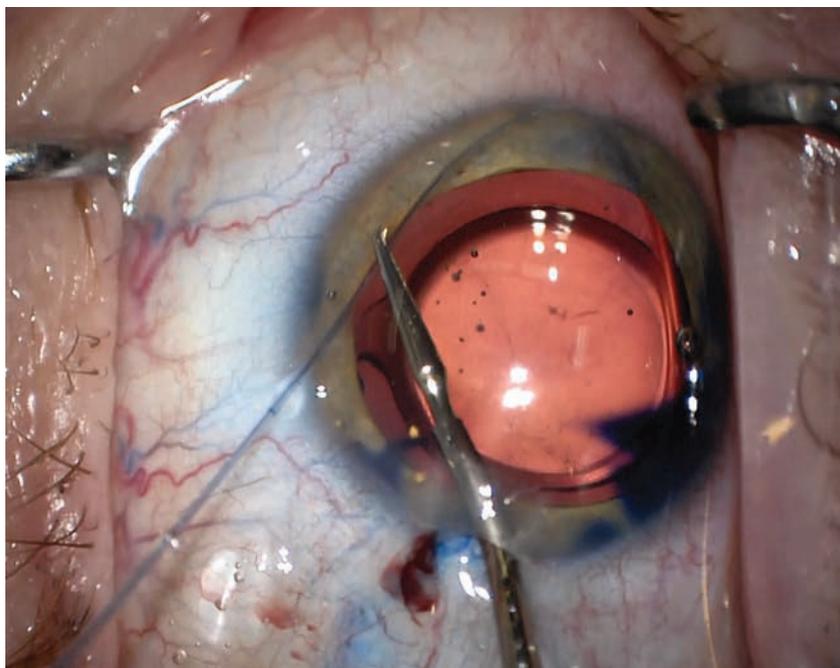
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This eye demonstrates large episcleral veins in the superior 180 degrees. Minimal staining is seen inferiorly, although this is thought to be where most of the collector channels reside.

GATT procedure, such as if the patient is taking anticoagulants or has a high risk of bleeding.)

The GATT procedure was initially introduced by Davinder Grover, MD, in 2014, using a full 360-degree unroofing of Schlemm's canal.⁵ In successful cases, that approach can result in a postop IOP very close to episcleral venous pressure, as low as 10 mmHg, although most of the time patients end up on fewer glaucoma medications with a postop IOP in the teens. We usually perform a hemi-GATT, meaning 180 degrees of treatment; our data suggests that this may be just as good (or almost as good) as doing a full 360 degrees, and it may lower the risk of hyphema.

We believe that adding the GATT procedure reduces resistance at the trabecular meshwork more than canaloplasty alone, especially for cases of secondary open angle glaucoma. Furthermore, performing a targeted, segmental GATT based on the patient's personalized aqueous

venographic pattern may increase our chances of success while reducing the risk of complications, since we're not unroofing all of Schlemm's canal. So far, we've been performing a full 360-degree venography, then following with a targeted hemi-GATT in the quadrants with a better aqueous venographic pattern (i.e., having more numerous vessels of larger caliber). Even if the trypan blue indicates limited functionality of the collector channels, we still tend to perform an inferior hemi-GATT, traditionally where there's a higher density of aqueous veins. We've found that even in these cases it may provide some benefit.

In terms of supporting data, we have a case series that has been accepted to the *Journal of Glaucoma* for publication. The data so far suggests that the double procedure is effective; it produces a statistically significant amount of pressure reduction, and a significant reduction in the number of medications patients need, including

a decreased need for acetazolamide, an oral carbonic anhydrase inhibitor that can be used as a last resort for lowering pressure in severe cases.

What's Next?

In addition to accumulating a larger database from which to draw conclusions about the dual procedure's effectiveness, we're hoping that the patterns of staining that appear may turn out to be connected to specific types of glaucoma; this may allow us to refine treatment based on the patterns we find.

It would also be helpful to develop a way to visualize the patency of the outflow system before performing the canaloplasty. That would allow us to show how much performing a canaloplasty affects the aqueous outflow patterns, and also guide us in terms of knowing which patients would benefit from this type of procedure, and which patients have a totally sclerosed or scarred physiologic outflow system and would be best treated with a gel stent, trabeculectomy or tube shunt. **REVIEW**

Dr. Gooi is an associate professor in the department of surgery at the University of Calgary in Alberta, Canada, where Dr. Docherty's work on this project was also conducted. Dr. Gooi has consulted for Aerie, Allergan, Bausch + Lomb, Glaukos, Latician, Salient and Santen. Dr. Docherty reports no financial conflicts.

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EyeArt AI Screening System for DR

Eyenuk recently received FDA clearance to market EyeArt, its autonomous AI (artificial intelligence) system for diabetic retinopathy. EyeArt can be used to detect more-than-mild DR and vision-threatening DR in the eyes of adults already diagnosed with diabetes who haven't been previously diagnosed with more-than-mild DR. In the clinical trial EyeArt demonstrated 96-percent sensitivity and 88-percent specificity for detecting more-than-mild DR, and 92-percent sensitivity and 94-percent specificity for detecting vision-threatening DR. The company says that EyeArt is able to detect both more-than-mild DR and vision-threatening DR in a single test, in primary- and eye-care settings. The AI system is compatible with the Canon CR-2 AF and Canon CR-2 Plus AF fundus cameras,

and the company plans to expand the number of compatible imaging devices. To learn more, visit eyenuk.com.

An Ergonomic Surgical Chair Inspired by Eye MDs

Every surgeon knows that having the right tool



for the job is essential—but what about the right chair? Haag-Streit says its new Core Surgical Chair was designed in collaboration with ophthalmologists, taking into account physicians' needs in the surgical suite. The company says the customizable curved backrest aligns the spine for added lumbar support and the chair's multi-directional adjustment makes it easy to position. Haag-Streit also notes that the chair is armless and has a narrow seatback to allow for freedom of movement without the risk of contamination. For information, or to schedule an evaluation, visit coresurgicalchair.com.

Eye Care On the Move

Olleyes has just released VisuALL, a portable, virtual-reality headset with AI technology for evaluating visual fields and visual acuity. The device enables eye-care providers to remotely monitor common diseases, says the company. Olleyes notes that patients can be tested in any lighting conditions with the Visu-

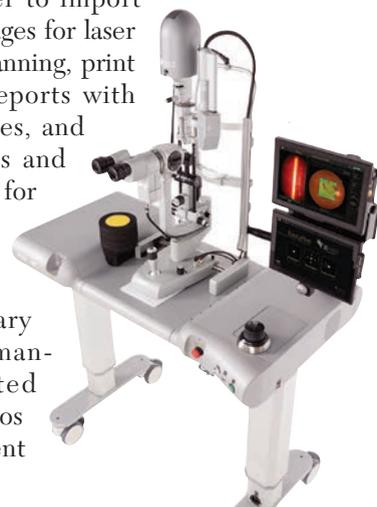


ALL's ambient control features, even in a fully illuminated waiting room. Olleyes notes that VisuALL can easily be disinfected for COVID-19 safety.

Olleyes has partnered with ophthalmic device-maker Keeler USA (a Halma company) for the distribution of the VisuALL in the United States. For information, visit keelerusa.com or call 1-800-523-5620.

A Mosar Makeover for Easyret

Mosar is a new, dedicated imaging system for Quantel Medical's Easyret yellow laser. This optional imaging system is FDA-approved and helps to enhance retinal laser treatment procedures and patient follow-up, according to the company. Mosar has three main user modes: a co-observation teaching mode for live viewing; an advanced mode that allows the user to import diagnosis images for laser treatment planning, print treatment reports with fundus images, and take pictures and record video for presentation and training purposes; and a library mode to manage collected images, videos and treatment



reports for exporting via USB or local network. For information, visit quantel-medical.com.

New Toric Lens Option from B + L

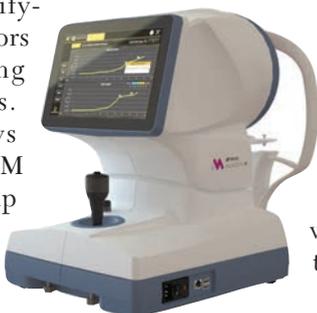
A new -2.75 D cylinder lens option is now available from Bausch + Lomb. The new lens is part of B+L's Biotrue OneDay daily disposable contact lens family and will be available for same-day fitting in a standard fit test. B+L says this lens will offer astigmatic patients the most toric parameters available in any daily disposable lens. The -2.75 D cylinder lens has a sphere power of plano to -6 D, in 0.5-D steps and will be available in axes of 10, 20, 90, 160, 170 and 180 degrees. B+L



adds that its astigmatic lenses feature a peri-ballast design and a tapered edge to limit lid interaction, and spherical aberration control to help reduce dysphotopsias. For information, visit biotruedailylenses.com.

Three Features for Aladdin-M

Topcon says its new Aladdin-M is a versatile instrument that includes corneal topography, pupillometry and optical biometry for myopia management, keratoconus screening and contact lens fitting. The instrument includes software for documenting axial length measurements over time, identifying risk factors and tracking Rx changes. Topcon says the Aladdin-M will also help eye-care profession-



als manage the growing myopia epidemic. For information, visit topcon-medical.com.

IOLMaster 700 Software Update 1.90 with Central Topography

Zeiss's latest software update for the IOLMaster 700 improves cataract workflow efficiency by providing more information about central corneal shape and making surgical planning data easier to access, according to the company. The update includes the Barrett True K with Total Keratometry formula and a



mobile app that allows cataract surgeons to transfer surgical planning data to the operating room from their mobile devices via the cloud.

For information about software update 1.90 with central topography, visit zeiss.com/iolmaster-topo.

Instrumental Changes

Beaver Visitech International's Malosa line of single-use instruments now includes specialty instruments for use in corneal refractive surgery. BVI says that the instruments in the Malosa line are made of high-quality surgical steel and provide a safe alternative to reusable instruments, reducing the potential for cross-contamination and the need for sterilization and repairs. For information, visit bvimedical.com.

Ready-made Patient PPE

In-clinic safety is a top priority for practices nationwide. To help ease patients' return to the office and streamline a time-consuming task, BVI now offers a simplified way for clinics and surgery centers to secure FDA-approved PPE for

patients. BVI says its Patient Packs are ready-to-use and include a face mask, bouffant cap, shoe covers and an optional isolation gown, along with easy-to-understand patient instructions. For more information, visit bvimedical.com.



Pain Relief for Genetic Disease Sufferers

Recordati Rare Diseases has just received FDA approval for Cystadrops (cysteamine ophthalmic solution 0.37%) for the treatment of ocular manifestations of cystinosis, a rare genetic condition present from birth that causes a body-wide buildup of cystine crystals, leading to tissue and organ damage. Those with ocular manifestations experience light sensitivity, eye discomfort and pain. Cystadrops is a viscous eye-drop solution that works by depleting the cystine crystal deposits in the corneas of cystinosis sufferers. Cystadrops is approved for four-times-daily dosing. For information, visit cystadrops.com. **REVIEW**





Updates from the PRO Study Group

A comprehensive look at how other retina specialists repair detachments can help inform your technique.

*Matthew Starr, MD, and Ata Salabati, MD, Philadelphia
Ed Ryan, MD, Minneapolis*

In the past, if you were a vitreoretinal surgeon looking for the best method for repairing a retinal detachment, the search for definitive data was frustrating, since most surgeons seemed to have a method that worked great for them but might not be reproducible by everyone else. Recently, however, the landmark Primary Retinal Detachment Outcomes (PRO) Study cut through a lot of the anecdotal noise and provided truly useful insights on such topics as the true value of scleral buckles in a surgical area dominated by vitrectomies (it turns out buckles are still very useful) and the results of detachment repair in phakic vs. pseudophakic eyes (the study found that one surgical method in particular is best for one of these groups).

To learn about all of the valuable data we've gleaned from this study that you can put to use in your practice, read on.

Differing Approaches

During the past 50 years, the preferred surgical method for repair of primary rhegmatogenous retinal detachment has shifted from scleral

buckles to pars plana vitrectomy, or combination PPV/SB. In 1980, PPV accounted for only 1 percent of all RRD surgeries, but by 2014 this percentage reached 83 percent.^{1,2}

The surgical approach for RRD differs amongst retina specialists; many will choose either SB, PPV or PPV/SB for the same anatomic presentation of RRD based upon their experience, preoperative factors and evidence in the literature. Specifically, many preoperative factors like the location and extent of retinal detachment, the patient's lens status, the location and number of breaks, and personal experience lead to the surgical plan, but there is still a lack of consensus among surgeons regarding the best approach.³ This discord is due to the difficulty in accounting for the many variables in surgical studies, such as draining of subretinal fluid, shaving of the vitreous base, preferred tamponade agent and the best amount of endolaser, among others.

Studies Lend Help

Though numerous studies have attempted to analyze surgical outcomes

for RRD repair, the Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment (SPR) study was perhaps the first and most important report on outcomes of various surgical approaches to RRDs. The SPR was a randomized, prospective clinical trial published in 2007 that showed the superiority of SB to PPV in visual acuity outcomes in phakic patients. The study also concluded that PPV was superior to SB in terms of anatomic outcomes for pseudophakic patients.^{4,5} This study, though, was carried out in the early 2000s before the widespread use of small-gauge vitrectomy and enhanced visualization systems, so more up-to-date studies are warranted. Also, it wasn't designed to compare PPV to PPV/SB.

This leads us to the Primary Retinal Detachment Outcomes study, in which we compiled a large, comprehensive, observational dataset from all patients at six centers who underwent primary RRD repair in 2015. Sixty-one vitreoretinal surgeons participated in the study, and the study centers spanned the United States, and consisted of:

- VitreoRetinal Surgery in Minneapolis;

Table 1. Summary of the Primary Retinal Detachment Outcomes Study's Six Reports

PRO Report	Purpose	Main outcomes
1	Describing the overall methodology of the study, evaluating data entry reliability, and reporting the overall success rate of the surgeries.	The precision of data entry was confirmed by inter-rater reliability (IRR), which showed strong agreement among raters. All three surgical methods (SB, PPV, PPV/SB) had a high single-surgery anatomic success rate.
2	To compare the anatomic and visual outcomes of the SB, PPV and PPV/SB surgeries in phakic patients.	In phakic, moderately complex RRD, SB and PPV/SB were superior to PPV in single-surgery anatomic success rate. SB showed the best visual outcomes compared to other methods.
3	To compare the anatomic and visual outcomes of the PPV and PPV/SB surgeries in pseudophakic patients.	Eyes undergoing PPV/SB compared to PPV alone had better anatomic outcomes, although the visual outcomes were similar in both methods.
4	To determine factors associated with 360-degree laser retinopexy and its effect on surgical outcomes.	Younger patients, surgeon preference, number of breaks, and the extent of detachment were associated with applying intraoperative 360-degree laser retinopexy. 360 laser may be associated with worse anatomic and visual results.
5	To evaluate the anatomical and visual outcomes of the non-complex RRD surgeries when using non-contact wide-angle visualization systems vs. wide-angle contact viewing system.	Anatomic success rates were similar using either viewing system. In the primary analysis, the contact lens system showed better visual outcomes compared to the non-contact method, but after controlling for confounding factors, the difference didn't remain statistically significant.
6	To compare anatomic and visual outcomes between primary PPV and combination PPV/SB for RRDs with inferior retinal breaks.	Retinal detachment with inferior retinal breaks had a higher single-surgery success rate if treated with PPV/SB compared to PPV alone. This difference in anatomic success was more prominent in phakic eyes.

- The Retina Center in Minneapolis;
- The Retina Institute in St. Louis;
- Mid Atlantic Retina/Wills Eye Hospital in Philadelphia;
- Associated Retinal Consultants in Royal Oak, Michigan, and;
- Massachusetts Eye and Ear Infirmary in Boston.

The PRO study group investigated the outcomes of RRD surgeries as no other series had done before. The study analyzed more than 250 pre-, intra- and postoperative metrics, attempting to identify any difference in surgical outcomes based on these metrics. The surgeons analyzed only primary rhegmatogenous retinal detachments that had not undergone previous attempts at surgical repair and excluded complicated retinal detachments such as those in the setting of penetrating injury, proliferative diabetic retinopathy, sickle cell disease, retinopathy of prematurity,

familial exudative vitreoretinopathy or ischemic vein occlusion, acute retinal necrosis and prior endophthalmitis. All in all, nearly 3,000 eyes recorded in the database had primary RRD repair with either SB, PPV, PPV/SB, laser retinopexy, cryopexy or pneumatic retinopexy.

To date, six publications have stemmed from the PRO database, with numerous other manuscripts either in-press or submitted to well-known ophthalmology journals.^{6,7(p2),8-11} The results of all six published papers are summarized in Table 1. Here's a look at each PRO study report and the unique insights it brought to vitreoretinal surgeons.

• **Report #1—Methodology.** This was first a methodology paper, but also highlighted overall non-comparative outcomes.^{6(p1)} First, regardless of the surgical approach, the overall success rate was high for primary RRD re-

pair. Second, more than half of the patients in this study were managed with primary PPV; primary SB was used in 13.5 percent of the cases, and 40.2 percent of the cases were managed with combination PPV/SB. These data underscore the importance of scleral buckling in the management of phakic retinal detachment. Lastly, this study analyzed data reliability using an inter-rater reliability (IRR) calculation factoring in 15 key variables to determine the consistency of data entry. The paper concluded there was a high degree of agreement in reliability of observations, giving reassurance that the data are trustworthy.

• **Report #2—Phakic outcomes.** The second PRO report focused on the visual and anatomic outcomes of phakic patients who underwent primary repair of RRD with PPV, SB or PPV/SB.^{7(p2)} For these patients, SB was superior to PPV in both anatomic and

visual outcomes, and PPV/SB was superior to PPV in anatomic outcomes. These results again highlight the importance of scleral buckling and the need to continue to educate future trainees on the intricacies of proper buckling techniques. Certainly, as a fellow I can appreciate the buckle training I'm receiving here at Wills Eye and know how important these buckles are to achieving anatomic and visual success. Even in the modern era of small-gauge PPV and enhanced wide-angle viewing systems, the results of the PRO study validate the continued use of scleral buckles in the management of RRDs.

- **Report #3—Pseudophakic outcomes.** The third PRO report focused solely on pseudophakic eyes undergoing either PPV or PPV/SB.^{8(p3)} SB wasn't analyzed separately, as only five pseudophakic eyes in the dataset underwent SB. This subset was composed of nearly 1,000 eyes, with 77 percent of the RRDs treated with PPV, and the remainder with PPV/SB. Patients undergoing combination PPV/SB were more likely to have inferior RRDs. This study again showed superior anatomic outcomes for PPV/SB versus primary PPV, but with no statistical differences in final visual outcomes between the cohorts.

- **Report #4—Surgical metrics.** Perhaps the greatest strength of the PRO database is the robust number of individual metrics collected for each surgery, which speaks to the effort of the hard-working researchers involved in the data-collection process. The first PRO paper to focus on the subset of metrics was PRO report number 4.^{9(p4)} The aim of this study was to assess outcomes in eyes that underwent intraoperative 360-degree laser retinopexy during repair of primary RRD with primary PPV or combination PPV/SB. Ultimately, 516 of 2,248 (23 percent) eyes underwent 360-degree laser retinopexy. Younger age, more retinal breaks, more extensive RRD

Table 2. Retinal Attachment Rates in the PRO Database

Procedure	Single surgery anatomic success	Final attachment success
SB	292/320 (91.2%)	315/320 (98.4%)
PPV	1011/1200 (84.2%)	1140/1200 (95%)
PPV/SB	735/815 (90.2%),	768 of 815 (94.2%)
Overall Study	87.3%	95.2%.

Table 2. Single-surgery anatomic success and final attachment success rates for all eyes, as well as analyzed by surgical method, within the Primary Retinal Detachment Outcomes (PRO) database.

and surgeon preference were significantly associated with the use of this procedure. However, when controlling for case complexity, intraoperative 360-degree laser retinopexy was significantly associated with lower final anatomic success and worse final visual acuity. Certainly these results are interesting and perhaps highlight the superior outcomes of a more targeted laser retinopexy during surgery. Within our practices, the choice of approach seems to be surgeon-dependent and is a question that will continue to be debated.

- **Report #5—Contact vs. non-contact lens viewing systems.** The fifth PRO report again used the vast metrics within the dataset to focus on outcomes of vitrectomies done with a contact versus a non-contact wide-angle lens during primary RRD repair.¹⁰

In this cohort, 363 eyes were treated using the contact lens system and 1,893 eyes treated with the non-contact viewing system. The initial analysis showed better final visual outcomes for the contact lens cohort, but after controlling for confounding factors, the difference didn't remain statistically significant. An analysis of anatomic outcomes showed no differences in single-surgery success or final anatomic success between the two viewing systems.

- **Report #6—Inferior retinal pathology and scleral buckles.** The sixth published manuscript answered the question of whether it's necessary to add a scleral buckle when repairing

RRDs with inferior retinal pathology.¹¹ Compared to previous papers on this topic that were more lenient in their grading of inferior pathology, the PRO manuscript only included eyes with retinal breaks found between the 5- and 7-o'clock meridians. The study included 238 eyes with inferior pathology and excluded primary scleral buckles. Ninety-five eyes (40 percent) underwent primary PPV and 163 (60 percent) that underwent combined PPV/SB. Combination PPV/SB had superior anatomic outcomes compared to primary vitrectomy, which remained significant when accounting for other preoperative metrics that may affect success, such as macula status, number of breaks, lens status, extent of detachment and surgeon factor. Subgroup analysis also showed that phakic eyes undergoing PPV/SB had superior single-surgery success rates.

Looking Ahead

The Primary Retinal Detachment Outcomes Study is a landmark database in vitreoretinal surgery. The use of a multicenter, multiple-surgeon, longitudinal analysis of outcomes of the repair of primary rhegmatogenous retinal detachments over a single calendar year gives the vitreoretinal community incredibly valuable insights. In particular, in the era of increasing use of small-gauge PPV for RRD repair, the PRO database reveals the continued usefulness of both primary and adjunctive scleral buckling for improved

anatomic and visual success, and underscores the added value of scleral buckles for the repair of primary rhegmatogenous retinal detachments. It's imperative that the next generation of vitreoretinal surgeons understands the nuances of proper scleral buckling technique given the outcomes identified in the PRO database, especially in phakic patients.

Moving forward, there are several other key projects coming from the PRO database that are analyzing various metrics within the rich dataset. Many reports are in press, specifically manuscripts focusing on the use of prophylactic ILM peeling during primary RRD repair, and repair of primary RRDs with concomitant, non-causal macular holes, as well as outcomes in younger and older patients with primary RRDs. These papers and others that delve into the different surgical approaches that lead to improved outcomes are on the horizon.

In the final analysis, the PRO database has been an excellent resource for retrospective cohort studies comparing multiple surgeons' approaches to the repair of many different types of primary RRDs with a variety of anatomic nuances. There will always be debate on how to best approach a particular surgical problem, and many surgeons can achieve the same outcome using vastly different approaches. The database highlights these different approaches, and in the era of increasing use of vitrectomy for the repair of primary RRD the study's outcomes remind us all of the continued importance of scleral buckles.

The database also allows critical examination of the various approaches the study's surgeons used to repair RRDs, and makes the results generalizable to the greater vitreoretinal surgery community. Even so, it remains difficult to design the perfect study of RRD treatment, given the inherent limitations of any research analyzing heterodox surgical techniques

and methods; each patient and surgical encounter is unique and requires a precise surgical plan. The PRO reports remain very useful for physicians, however, and we hope that this review of these and future PRO manuscripts will help guide vitreoretinal surgeons moving forward. **REVIEW**

Dr. Starr is a surgical retina fellow in the retina service at Wills Eye Hospital/ Mid Atlantic Retina in Philadelphia. Dr. Salabati is a research fellow in the retina service at Wills Eye Hospital/ Mid Atlantic Retina in Philadelphia. Dr. Ryan is an associate clinical professor of ophthalmology in the University of Minnesota Department of Ophthalmology.

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An older patient with a history of cataract surgery with adjunctive MIGS presents with hypotony and decreased vision.

Vikram A. Shankar, MD, MPH, and Reza Razeghinejad, MD

Presentation

A 62-year-old male was referred to Wills Eye Hospital for hypotony and decreased vision in the left eye after routine cataract surgery and iStent placement 18 months prior by an outside ophthalmologist. Ocular history was notable for primary open angle glaucoma in both eyes, managed with latanoprost in the right eye only.

After the cataract surgery, although vision was 20/25, intraocular pressure had fallen to 8 mmHg without evidence of hypotony maculopathy. Initial gonioscopy showed a well-positioned iStent implant in the trabecular meshwork, and the patient was monitored without intervention. Over the next several months, the patient’s visual acuity and IOP remained unchanged as postoperative medications were tapered.

Five months after surgery, the patient’s vision suddenly declined to 20/200 despite no meaningful change in IOP. He denied associated headaches, eye pain, photopsias or floaters. He was referred to a local retina specialist after an optical coherence tomograph of the optic nerve and macula demonstrated changes consistent with hypotony maculopathy (Figure 1). His low IOP was attributed to the iStent, and he was scheduled to have it explanted. Despite successful removal of the stent several days later, his postop IOP remained between 6 and 8 mmHg, and his vision failed to improve. He was subsequently referred to the Wills Eye Hospital Glaucoma Service for further management.

Medical History

Past medical history included gastroesophageal reflux disease, Crohn’s disease and attention-deficit hyperactivity syndrome. His past surgical history was notable for cataract extraction and intraocular lens placement in the right eye several years prior, in addition to the recent CE/iStent procedure in the left eye. Family and social histories were noncontributory, and he reported no drug allergies. Oral drugs included dexlansoprazole, adalimumab, escitalopram and atomoxetine. At the time of his presentation, his only ocular medication was latanoprost in the right eye.

Examination

Ophthalmologic examination revealed a best-corrected visual acuity of 20/20 OD and 20/400 OS. The patient’s pupils were equal, round and reactive to light without an afferent pupillary defect. IOPs were 14 mmHg OD and 8 mmHg OS. Extraocular motility was full in both eyes, but the patient was unable to perform confrontation visual fields and color plates OS. Slit lamp exam demon-

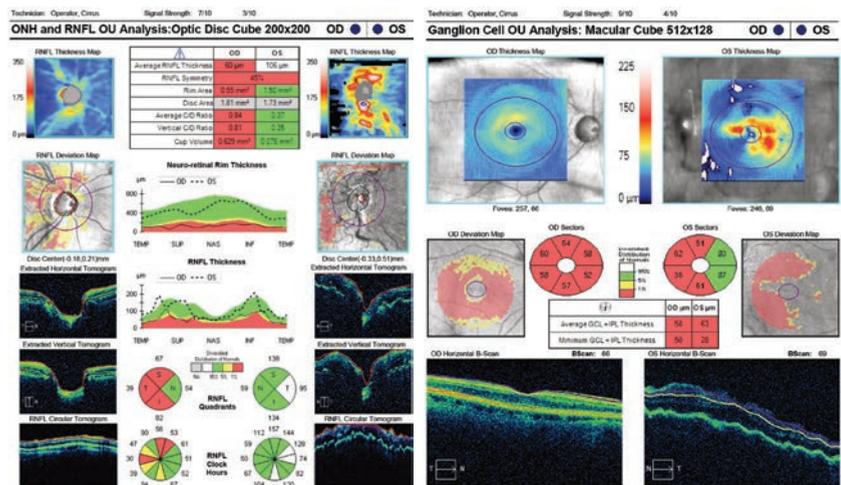


Figure 1. (Left) Cirrus OCT of the optic nerve head and retinal nerve fiber layer of the hypotonous left eye demonstrates pseudo-reversal of optic nerve cupping due to distortion of choroid and retina with accompanying vascular tortuosity. Disruption of normal optic nerve and retinal anatomy precludes any assessment of glaucomatous damage to the RNFL. (Right) Chorioretinal folds are observed in the macula of the left eye consistent with hypotony maculopathy.

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strated a moderately deep and quiet anterior chamber bilaterally, with well-centered intraocular lenses in the capsular bag OU. Surgical wounds were Seidel negative in both eyes. Funduscopy exam of the right eye demonstrated previously known optic nerve cupping with an otherwise normal macula and retinal periphery. The left eye demonstrated diffuse, horizontally-oriented chorioretinal folds, tortuous and enlarged retinal vessels, and optic nerve head swelling.

Based on this information, what's your diagnosis? The diagnosis appears below.

Workup, Diagnosis and Treatment

The initial differential for postoperative hypotony is broad, and includes inflammation, uveitis, wound leak or inadvertent bleb formation, cyclodialysis clefts, ciliochoroidal or retinal detachments, and cyclitic membrane. Broadly, the pathophysiology underlying hypotony can be divided into mechanisms of decreased aqueous production, increased aqueous outflow or a combination of the two. Easily investigable causes such as intraocular inflammation, wound leak and bleb formation were ruled out with the patient's initial slit lamp examination. Furthermore, the initial funduscopy exam failed to reveal choroidal or retinal detachments.

Gonioscopy revealed a nasal cyclodialysis cleft in the left eye between 9:45 and 11:30. Angles were otherwise found to be open to D40f2+ OD and (C)D35f2+ OS as graded by the Spaeth gonioscopy grading system. The extent of the cleft and associated suprachoroidal effusion was confirmed with ultrasound biomicroscopy (Figure 2). The patient was initially started on atropine drops two times daily for six

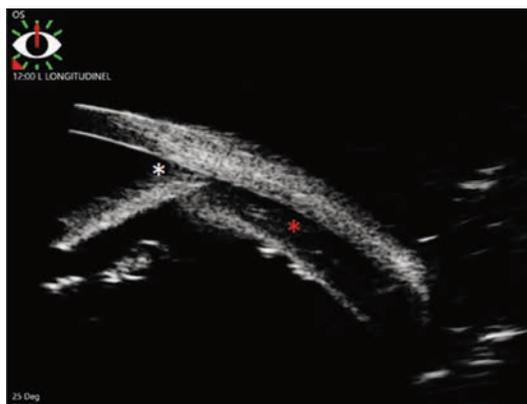
weeks without improvement. This was followed by three sessions of argon laser treatments to the cyclodialysis cleft. However, vision and IOP remained unchanged and repeat gonioscopy confirmed persistence of the cleft.

Given the failure of conservative treatment options, an *ab-externo* cyclodialysis cleft closure was attempted through a partial thickness limbal scleral flap. Surgery was performed without complications, but postoperative gonioscopy revealed only partial closure with a persistent cleft between 8:30 and 9:30. Cycloplegics were restarted, but the cleft failed to resolve after observation for nine weeks and no improvement in IOP or vision was noted.

An *ab-interno* cyclopexy was then attempted. On postop day 1, IOP rose to 36 mmHg and slit lamp examination demonstrated patchy corneal microcystic edema and a deep anterior chamber with trace cells and flare. Gonioscopy subsequently confirmed closure of the cyclodialysis cleft. The IOP lowered with topical medications. Two weeks

postoperatively, the patient presented for follow-up with worsening headaches and an IOP of 59 mmHg despite therapy with dorzolamide/timolol and netarsudil. Maximal medical therapy was initiated, but IOP remained elevated to 30 mmHg nearly a month later with little improvement in his persistent choroidal folds. He underwent Baerveldt tube shunt placement and his IOP subsequently improved to 12 mmHg. On his most recent follow-ups, vision OS had improved to 20/100 and IOP was stable between 11 and 12 mmHg.

Figure 2. Ultrasound biomicroscopy of the left eye demonstrates the cyclodialysis cleft with an area of separation of the ciliary body from the sclera (white asterisk). Significant fluid in the suprachoroidal space through *ab-interno* drainage from the anterior chamber is also identified (red asterisk).



Discussion

Cyclodialysis clefts are a rare sequela of accidental or iatrogenic trauma, characterized by a separation of the ciliary body from its attachment to the scleral spur.¹ Although previously observed only as a result of blunt trauma to the globe, a cyclodialysis cleft may also occur as a complication of any anterior segment surgery, particularly cataract surgery, goniotomy and iridectomy.² Clefts provide an alternate outflow path for aqueous humor to the suprachoroidal

space, which can result in chronic hypotony with potentially irreversible morphologic changes to the globe.^{1,3} However, as illustrated in this case, hypotony is not always symptomatic, and no pressure cutoff necessitates intervention in the absence of clinical signs of hypotony maculopathy. Generally, these patients present with visual decline from secondary changes in the structure of the eye including corneal edema and with-the-rule astigmatism, optic disc edema, maculopa-

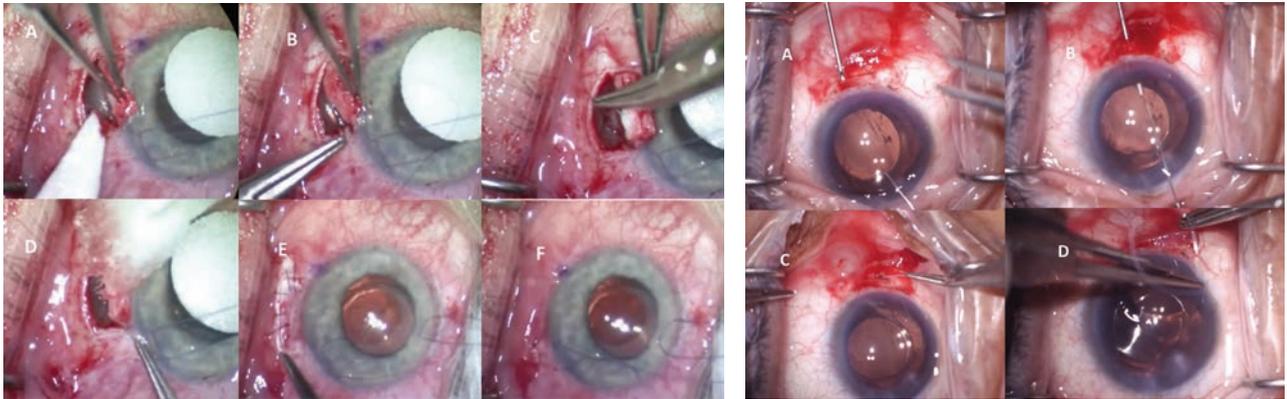


Figure 3. Intraoperative photographs of *ab-externo* cyclopexy utilizing full thickness (images on the left) and partial thickness (images on the right) scleral flaps. Sutures are passed through the cleft and ciliary body under direct visualization.

thy, choroidal folds or ciliochoroidal detachments.^{4,5}

Clefts may be difficult to identify on gonioscopy, particularly in patients with a shallow anterior chamber or corneal edema. Intracameral injections of viscoelastic may be used to reform the AC and improve visualization of the angle. In some patients with shallow chambers, indentation gonioscopy may help detect the cleft. Although dynamic gonioscopy remains the gold standard in diagnosis, imaging with anterior segment OCT or ultrasound biomicroscopy may be valuable in patients in whom the view of the angle is compromised.^{4,6} These imaging modalities can delineate even small cyclodialysis clefts, and UBM in particular boasts excellent sensitivity for clefts that may be missed on gonioscopy without AC reformation.⁶

Cyclodialysis clefts may be managed with medical, laser or surgical techniques, with the choice of therapy titrated to clinical severity. Smaller clefts, often defined as fewer than four clock hours, may resolve with medical cycloplegia.¹ Cycloplegics such as atropine 1% help dilate the ciliary body ring and promote apposition of the detached muscle to the sclera.⁷ These drugs may be tried for six to eight weeks while tapering or discontinuing steroids to promote adhesion and fibrosis.^{1,7} Patients who fail medical management may be candidates for noninvasive laser techniques that promote local inflammation within the cleft. Argon laser,⁸ diode endophotocoagulation, trans-scleral diode^{9,10} and Nd:YAG laser have been employed, but success rates are modest and definitive closure with laser alone is reported to occur in less than 20 percent of cases.^{1,7}

For patients who fail conservative management, fixation of the detached ciliary body to the scleral bed, known as cyclopexy, is the definitive treatment.¹¹ A large multicenter series reported closure rates of greater than 96 percent for cyclopexy, although a lack of standardization in surgical nomenclature renders comparison of different surgical methods difficult.^{1,4} Traditional suture fixation may be performed through external (*ab externo*) or internal (*ab*

interno) approaches. The *ab-externo* approach may be performed through either full or partial-thickness scleral flaps with direct visualization and suturing of the detached ciliary body (Figure 3). Various authors have described excellent surgical outcomes with variations of this technique, although complications such as hemorrhage, hypotony, retinal detachment and endophthalmitis have also been reported.^{2,5} *Ab-interno* approaches avoid the need for a full-thickness scleral cut-down and instead use sutures carried out from an opposite clear corneal incision (Figure 4).^{2,3}

Surgical methods that employ mechanical tamponade of the ciliary body through either internal or external approaches have also been described. Internal tamponade may be successfully performed with the haptics of a sulcus intraocular lens or capsular tension ring (e.g., the Cianni ring).² These devices may have more predictable outcomes than direct suturing and may be superior for extensive clefts; however, they also carry risks of ciliary body injury, erosion, pain and hemorrhage. External tamponade with anterior scleral buckling and silicone tubes and sponges offer less-reliable outcomes and may induce astigmatism, intolerable foreign body sensation or exposure of the implant.^{1,4} Pneumocyclopexy using intravitreal SF₆ or C₂F₆ gas has also been explored, but is less-commonly used given the necessity for coordination between anterior and posterior segment surgeons.^{3,12}

Postoperatively, successful closure of a cleft may be marked by an IOP spike that requires close monitoring and possible resumption of ocular hypotensive medications.^{2,13} These spikes are attributed to trabecular dysfunction and Schlemm's canal collapse in the setting of the alternate aqueous outflow path. In our patient, even after resumption of topical glaucoma therapy, a Baerveldt tube shunt was eventually required to return IOP to the target range. Although long-standing maculopathy may not be reversible due to chronic fibrosis and distortion of the retina and choroid, most patients, including our own, demonstrate

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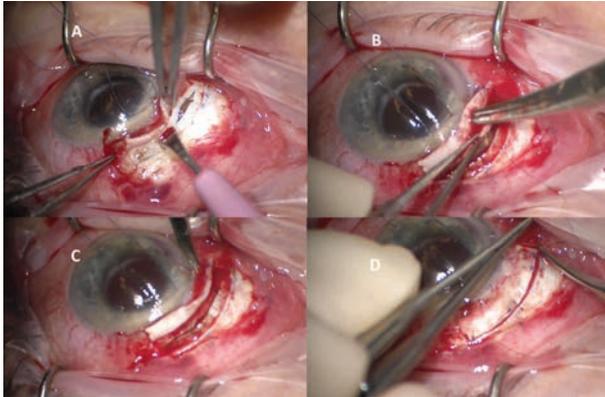


Figure 4. Intraoperative photographs of *ab-interno* cycloplexy with a partial thickness scleral flap elevated over the cleft. Suturing is carried out through an opposite clear corneal incision without direct visualization of the cleft.

improvement in vision after reversal of low IOP.^{3,13}

Although minimally-invasive glaucoma surgery is gaining popularity in patients with mild or moderate glaucoma, these procedures—indeed, any anterior segment surgery—may result in iatrogenic damage to angle structures and creation of cyclodialysis clefts. Despite a growing body of literature regarding management, considerable ambiguity remains regarding the ideal timing and method of treatment. Conservative approaches with cycloplegics and laser are appropriate in the absence of visual changes. However, clinical evidence of hypotony should be addressed with cycloplexy in an efficient timeframe to minimize risk of permanent structural damage to the eye. Further investigation and long-term studies are still needed to evaluate the myriad surgical techniques for cleft closure, with the eventual goal of creating well-defined treatment algorithms for this rare complication. **REVIEW**

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XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS

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

- Hypersensitivity [see *Contraindications (4)*]

6.1 Clinical Trials Experience

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

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

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

6.2 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to

pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear [see *Clinical Pharmacology (12.3)* in the full prescribing information].

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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as early as 2 weeks.^{3*†}

xiidra[®]
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Not an actual patient.

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).³

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. **Pivotal trial data:** The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study endpoints included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).³

A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.³

Indication

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

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

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

References: **1.** US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=349&showFR=1> **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.

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