REVIEW® of Ophthalmology

November 2019

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CORNEA: From Front to Back

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INDICATIONS: The TECNIS Symfony® Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model ZXR00 IOL is intended for capsular bag placement only. **WARNINGS:** Patients with any of the conditions described in the Directions for Use may not be suitable candidates for an intraocular lens because the lens may exacerbate an existing condition, may interfere with diagnosis or treatment of a condition, or may pose an unreasonable risk to the patient's eyesight. Lenses should not be placed in the ciliary sulcus. May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL; fully inform the patient of this risk before implanting the lens. Special consideration should be made in patients with macular disease, amblyopia, corneal irregularities, or other ocular disease. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including: a perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low- illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL. **SERIOUS ADVERSE EVENTS:** The most frequently reported serious adverse events that occurred during the clinical trial of the TECNIS Symfony® lens were cystoid macular edema (2 eyes, 0.7%) and surgical reintervention (treatment injections for cystoid macular edema and endophthalmitis, 2 eyes, 0.7%). No lens-related adverse events occurred during the trial.

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ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

REFERENCE: 1. DOF2018CT4021. Johnson & Johnson Surgical Vision, Inc; 2018.

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REVIEW NEWS
Volume XXVI • No. 11 • November 2019

New AMD Drug Beovu Aims For Less-Frequent Dosing

In early October, Novartis received FDA approval for the Beovu (brolucizumab) injection, previously known as RTH258, for treating neovascular age-related macular degeneration. Significantly, brolucizumab allows for three-month dosing intervals after a three-month loading phase. Some hope that fewer patients may be lost to follow-up with brolucizumab since fewer doses are required, compared to current anti-VEGF agents which have four-week dosing periods. The frequency of a monthly injection often creates a burden for patients suffering from chronic conditions.

Brolucizumab is a single-strand antibody fragment that works by delivering a high concentration of drug to the target area, explains Pravin U. Dugel, MD, managing partner at Retinal Consultants of Arizona and clinical professor at the Roski Eye Institute, Keck School of Medicine, University of Southern California. Dr. Dugel was the principal investigator in Novartis' HAWK trial of brolucizumab, and consults for the company. "For a long time, single-strand antibody fragments couldn't be developed because of aggregation and solubility issues," Dr. Dugel notes. "But a company in Zurich called Esbatech developed a way to make single-strand antibody fragments that overcame the solubility and aggregation challenges." Esbatech was later acquired by Alcon.

The small size of single-strand antibody fragments is the key to brolucizumab's effectiveness, Novartis says, since it allows for enhanced tissue penetration and drug delivery, and provides more active binding agents than other anti-VEGFs. "Brolucizumab is very small—only 26 kDa—and can be delivered to the target at about 12 times the molar concentration of Eylea," Dr. Dugel explains. "This means is that there's much more drug where we need it."

The Phase III HAWK and HARRIER studies were randomized, double-masked multicenter head-to-head trials for patients with wet AMD; they included more than 1,800 patients across nearly 400 centers around the world. The studies were designed to compare the efficacy and safety of brolucizumab 6 mg (both studies) and 3 mg (HAWK only) versus aflibercept 2 mg in patients with wet AMD. Brolucizumab met its primary endpoint of noninferiority versus aflibercept in mean change in best-corrected visual acuity at year one, despite the fact that more than half of the patients were treated every 12 weeks, compared to every eight weeks with Eylea during the maintenance phase, says Dr. Dugel.

In the Phase III clinical trials, brolucizumab produced a greater reduction in central subfield thickness and subretinal fluid than aflibercept. Looking ahead to how clinicians might employ the new treatment, Dr. Dugel says, "We'll probably use it the same way we use current drugs, which is mainly the treat-and-extend strategy."

Dr. Dugel explains that OCT was used as a biomarker in the Phase III studies for measuring retinal thickness and checking for the presence of fluid as a sign of disease activity. "The OCT [scans are] the only objective biomarker for disease activity we have," he says. "We base our decisions to treat or not to treat mainly on the OCT."

In the HAWK and HARRIER studies, more fluctuations in the OCT data were observed with Eylea than with brolucizumab, says Dr. Dugel. "Fluctuations seen on OCT may be an indication of disease control," he adds. "Analyses in two separate level 1 studies (CATT and IVAN) found that in a dose-dependent manner, the more fluctuations you have in the OCT, the worse your vision. Novartis repeated this analysis in the HAWK and HARRIER studies and found the same thing. All of these analyses were agnostic of the drug, so now we've got four level-one studies (CATT, IVAN, HAWK and HARRIER) with evidence that, in post hoc analyses, the more fluctuations you have—that is, the less disease control you have—the worse your vision will be." Observers point out, however, that differences in mean OCT fluctuations are only potentially meaningful if all arms are getting the same, fixed dosing regimen. Because the brolucizumab arm is a blended q8/q12 with patients changing from 12 to eight weeks at various time points over the course

(Continued on p. 6)

Matthew Chapin • Andover, Mass.

How to Use the FDA Ophthalmic Monograph

In this installment of OPDI, we describe the basics of the ophthalmic monograph and its implications for product development. While this monograph has been in place for many years, our research and consulting group often receives questions from new entrepreneurs (and even experienced developers) regarding what the monograph is/isn't and how it applies in specific situations. Here, we'll provide some background and attempt to correct a few common misconceptions.

What is the Monograph?

In 1983, the U.S. Food and Drug Administration issued a proposed rulemaking in the form of a tentative monograph to establish conditions by which over-the-counter ophthalmic products are recognized as safe and effective and not misbranded. The FDA then issued this as a final monograph in 1988 (21 CFR 349).

21 CFR 349.1 starts by stating: "An over-the-counter ophthalmic drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part and each of the general conditions established in 330.1." In other words, if one follows the specifications of the regulation, a New Drug Application isn't required for FDA review of products which contain the monograph-specified active ingredients, the indication for use, and labeling.

There are six defined categories of active ingredients listed in the monograph: demulcents; astringents; emollients; hypertonicity; vasoconstrictors; and eyewashes. Within each category there are specified active ingredients and concentration ranges that are acceptable for use. For each category of active ingredient, the monograph specifies the acceptable language that can be listed as the indication on the label. For example, hypromellose in the range of 0.2 to 2.5% can be labeled "For use as a lubricant to prevent further irritation or to relieve dryness of the eye." For each category there is a specified wording that's deemed acceptable as a statement of identity, indication, warnings and directions. There's also an allowance in 21 CFR 349.30 for specified combinations of two—or in some cases more—listed ingredients.

Implications for OTC Products

Referring to drug products, there are two pathways for development and marketing of OTC products in the United States, 1) monograph; and 2) following the NDA (or 505b2) pathway.

Products that follow the monograph aren't reviewed by FDA prior to marketing. There are standard requirements for labeling, such as those for expiration dating based on stability data, labeling requirements per 21 CFR 201.66 and the requirement that the products are made according to Good Manufacturing Practices. But there's no formal review by the FDA like there is a for a new drug product with an NDA. Manufacturers are responsible for ensuring quality and a compliant product. Keep in mind that while there isn't a formal FDA review or requirement for it, distributors may have a separate need for a certain amount of stability to support desired shelf life and inventory, and therefore it's the manufacturing that's generally the rate-limiting step when launching a new OTC monograph product. Note that adhering to 21 CFR 349.1 assumes the drug maker is also following CFR 330.1, which, among other labeling mandates, requires that the facility at which the product is manufactured be registered, and the product listed in compliance with part 207 of the chapter. (Part 207 covers requirements for manufacturing establishment registration and listing of the drugs to obtain a National Drug Code.) The monograph also mandates that the product only contain suitable inactive ingredients that are safe and don't interfere with the product's effectiveness.

While this article isn't intended to be an extensive review of formulations, a brief note on inactive ingredients: For a monograph product, inactive ingredients can be chosen from the current FDA database. This lists substances generally known to be safe in certain concentrations/amounts and for certain methods of dosing. Ingredients are added to the list after being formally reviewed as part of past NDAs for other products.

Existing OTC products generally fall under the monograph, meaning there was no formal review by the FDA in advance. One example of a non-monograph product that was a direct-to-OTC NDA product, however, is Lumify (brimonidine 0.025%, Bausch + Lomb). B+L used the extensive history of safety of Lumify's active ingredient at higher concentrations to obtain approval based on a clinical program for redness relief. The antihistamine ketotifen is another example of a current OTC, but non-monograph, ingredient. For example, Alaway (ketotifen 0.025%, B+L) was a reformulation of an already approved and marketed product (containing the antihistamine ketotifen), using the same concentration of the active ingredient. This was approved based on a single bioequivalence trial using the standard conjunctival allergen challenge clinical model for allergy.

Common Misconceptions

One question we frequently receive is: If a product changes some ingredients, but they're still contained in the monograph, do clinical studies need to be performed, or can one make those changes and just launch a product? We've heard this asked both for OTC and Rx products. The short answer is that such changes can't simply be made without filing to the FDA with supportive clinical data. The FDA views any changes in OTC or Rx formulations, including changing into/out of an inactive ingredient, or modification of concentration (including simply removing a preservative) as a change that may impact the pharmacokinetics of the active ingredient, and thus efficacy and safety. A change in preservative may impact penetration of the drug; changing a demulcent could impact viscosity and dwell time of the drug, impacting PK; and even simple changes in a buffer can impact comfort.

(Continued on page 6)

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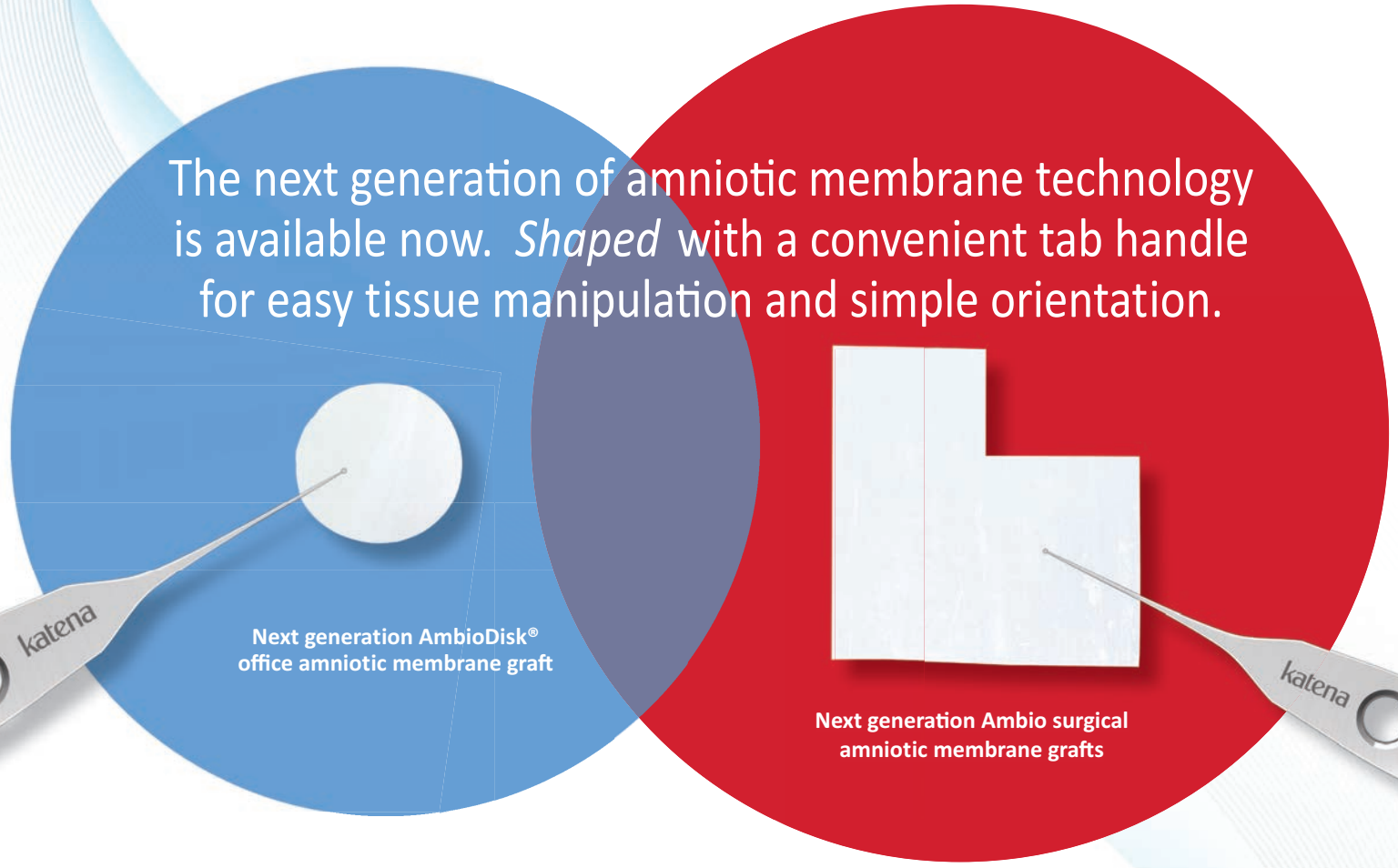

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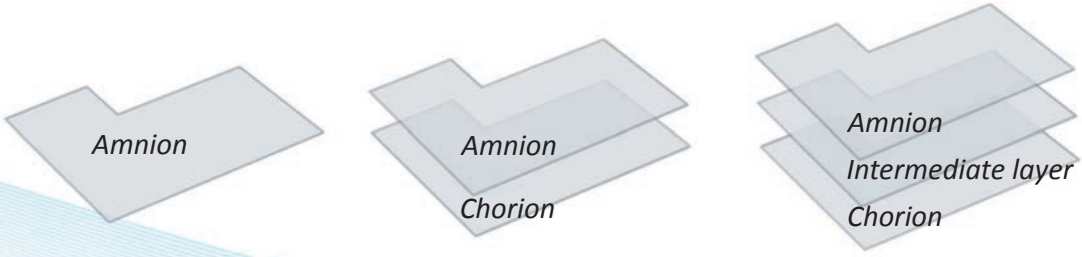

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REVIEW OPDI

(Continued from page 4)

Therefore new formulations (even altering an ingredient from the monograph list that's in the product as an inactive ingredient) require submission of clinical data. Such a change would go through the NDA (or 505b2) process. In some cases, all that might be needed is a single clinical trial as a pathway for FDA review. In our May 2018 column, we discussed the 505b2 pathway, which allows applicants to reference other data in their submission, including already published data or data from a prior review by the FDA. Such a discussion is beyond the scope of this article, however.

Another question is: For a given non-monograph product (Rx or OTC), if one adds a monograph ingredient, can the monograph label indication be included in the labeling of the product? Again, the short answer is no. If a product was approved by FDA as non-monograph (whether due to an ingredient or indication that's non-monograph), and a formulation change is being pursued, then it needs to follow requirements for an NDA pathway (or 505b2 as applicable). Note that the monograph is different from developing and gaining approval of a generic under 505(j) as an Abbreviated New Drug Application (ANDA); that's used for generic products with non-monograph active ingredients.

From a development perspective, the monograph provides flexibility for marketing products that consist of well-known ingredients, and streamlines the labeling. Of course, one has to thread the needle between time, cost and differentiation, and develop the reason-to-believe and positioning for new monograph formulations, to ensure you get the maximum value. This has been achieved, for example, with tear substitutes, all of which currently fall under the monograph, yet many have differentiated clinical performance characteristics. If you have questions about the nature of specific ingredients, labeling or pursuing monograph deviation, we, as always, encourage early interaction with the FDA.

Mr. Chapin is senior vice president of corporate development at Ora, which offers device and drug consulting, as well as clinical research and development. The author welcomes your comments or questions regarding product development. Please send correspondence to mchapin@oraclinical.com or visit oraclinical.com.

REVIEW News

(Continued from p. 3)

of the study, that alone may smooth the mean OCT curve and blunt the fluctuations that may or may not be present, so one can't really can't claim fluctuation differences with certainty in HAWK and HARRIER.

Brolucizumab is contraindicated in patients with ocular or periocular infections and active intraocular inflammation, according to Novartis. Dr. Dugel reports that no significant adverse side effects or events turned up in the studies.

The most common adverse events (occurring in 5 percent of patients) included blurred vision, cataract, conjunctival hemorrhage, vitreous floaters and eye pain, but Dr. Dugel notes that "none of these were out of line with other anti-VEGF side effects. There are always some adverse events with any biologic," he says.

The next step for brolucizumab will likely involve the drug being used to treat wet AMD patients who still have fluid despite their current treatment regimen. Dr. Dugel says the first patients who will get this drug will probably be the ones that physicians have treated for six months or a year without fluid resolution. "We'll see if brolucizumab can offer better disease control," he says. "The Phase III studies weren't done on these types of patients, but we'll also use brolucizumab in the clinic on treatment-naïve patients, as we did in the studies."

Dr. Dugel says we can look forward to additional study results for brolucizumab. A head-to-head study versus Eylea for macular degeneration called MERLIN is currently recruiting patients, and a treat-and-extend study called TALON is also recruiting. For its use in diabetes, KITE and KESTREL are ongoing, says Dr. Dugel. "We have more data for brolucizumab than any other drug I know at launch, so we won't have to guess or extrapolate too much." REVIEW

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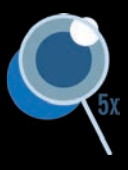

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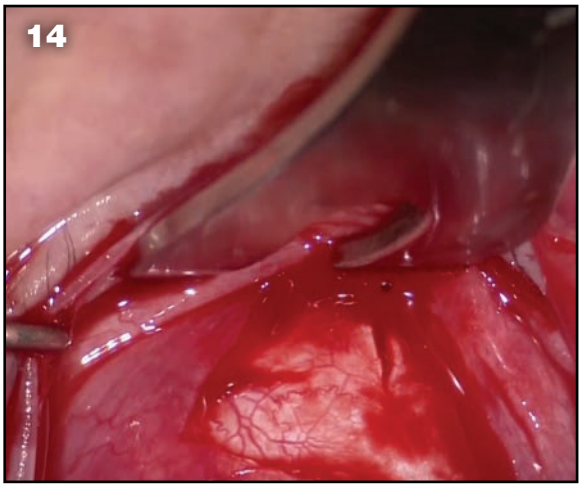

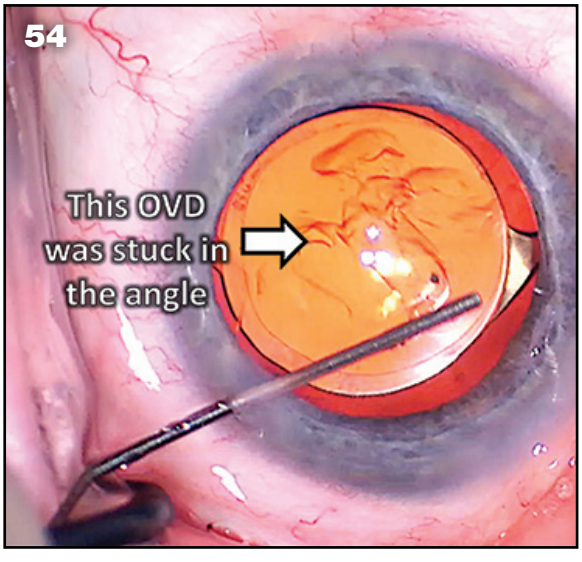

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To fight back against the impact of this disease, focus on early diagnosis, active monitoring, and prompt medical intervention.[1,3-5]

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HORIZON

Dealing with a Rare Complication

How to manage suprachoroidal hemorrhage—a rare complication that most surgeons will face at least once in their careers.

Kavitha R. Sivaraman, MD
Cincinnati

A suprachoroidal hemorrhage is one of the most dreaded surgical complications an anterior segment surgeon can face. Although more frequently encountered when large-incision intracapsular and extracapsular cataract extractions were commonplace, this potentially catastrophic event can occur even during routine, small-incision phacoemulsification.

Here, we'll review the risk factors and pathophysiology of this potentially devastating complication and offer advice on how to recognize and respond to it. Included are strategies for following up in the hours and days after a suprachoroidal hemorrhage.

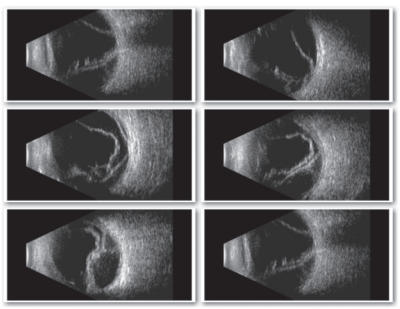
What the Evidence Tells Us

Most studies of SCH during cataract surgery don't distinguish between phacoemulsification and ECCE. Estimates of its incidence range from 0.04 to 0.26 percent.[1,2,3,4] A Swedish study reported a 0.03 percent incidence of SCH among a cohort of more than 23,000 eyes undergoing phacoemulsification surgery, which is about three per 10,000 cases.[5] These numbers may be falsely reassuring—although the risk of SCH may be very low for any case, most cataract surgeons will have to contend with a case at some point.

Risk Stratification

Risk factors for intraoperative SCH are categorized as systemic, ocular or intraoperative. (*See Table 1, page 16.*) Although most of these risk factors aren't modifiable, you can control two notable exceptions: those associated with systolic blood pressure and heart rate. Both are important perioperative considerations for optimization, especially in an already high-risk patient.

The common thread connecting all risk factors listed table 1 is that they predispose a patient to rupture of a ciliochoroidal vessel, either because of structural weakness of the vessel or because of an increasing pressure gradient between the choroidal vasculature and the vitreous cavity. Once a vessel ruptures, rapid accumulation of blood occurs in the suprachoroidal space. Arterial and venous suprachoroidal bleeds can occur. Bleeding from an arterial hemorrhage accumulates much more rapidly, causing an elevation of the overlying and adjacent retina and choroid, which can then stretch, leading to the rupture of additional ciliary vessels. If all wounds are secured, IOP will rise and the accumulating hemorrhage will self-tamponade. If wounds remain open, extrusion of intraocular contents can occur.



Jonathan Tzu, MD

Figure 1. B-scan ultrasound after drainage of suprachoroidal hemorrhage shows resolution of hemorrhage but development of a total retinal detachment.

Intraoperative Warning Signs

An SCH can occur at any time during surgery. However, one study found the highest incidence (around 35 percent) during irrigation/aspiration after nucleus removal. The telltale sign of a developing hemorrhage is a darkening

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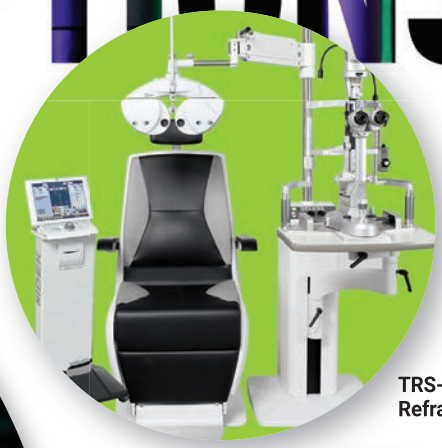

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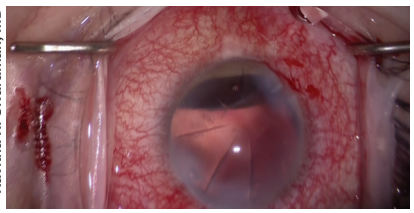
Table 1. Risk Factors for Intraoperative Suprachoroidal Hemorrhage[6,7]

Systemic	Ocular	Intraoperative
Advanced age	Glaucoma	Large incision
Atherosclerosis	High preoperative IOP	Hypotony
Hypertension	SCH in fellow eye	Valsalva maneuver
Tachycardia	Axial myopia	Open posterior capsule



Kavitha R. Sivaraman, MD

Figure 2. Loss of red reflex in the nasal quadrant due to formation of a suprachoroidal hemorrhage during cataract surgery.

or distortion of the red reflex, often moving from one end of the eye to the other, although it can also remain in one quadrant. The anterior chamber can shallow, sometimes abruptly, particularly if the eye is hypotonous.

IOP can spike, leading to a "rock-hard" globe and acute pain, especially if surgery is performed under topical anesthesia. Patients often complain of pain from concomitant stretching of the supraciliary nerves. They may involuntarily bear down, adding to the posterior pressure and pain. Intraocular viscoelastic may expulse, and the iris and IOL may prolapse. If the patient develops a capsular or zonular breach, look for vitreous presentation.

The hemorrhage may appear as a brownish, dome-shaped elevation on indirect ophthalmoscopy. But don't stop to visualize it until you have secured the globe, as described below.

Responding to an SCH

At the first indication of a possible SCH, your most critical and time-sensitive priority should be to withdraw your surgical instruments and achieve a watertight closure of all surgical wounds. (*Table 2 below outlines basic guidelines for responding when you suspect this emergency.*) If a wound remains open in the presence of an expansile SCH, you risk the extrusion of intraocular contents. Immediately suturing the wounds is particularly important during planned ECCE or conversion to ECCE from phacoemulsification, due to the larger incisions, which may not be self-sealing.

Although we're conditioned as surgeons to avoid leaving nuclear material in the eye, you must resist the urge to finish the cataract procedure. Trying to remove remaining lens material increases the risk of a progressive SCH and subsequent loss of intraocular contents. When confronted by active suprachoroidal bleeding, particularly arterial bleeding, you won't be able to infuse fluid fast enough to counteract the expansile forces of the hemorrhage. Arterial blood pressure is higher than infusion pressure, meaning fluid will be displaced back up the phaco tubing as the hemorrhage progresses. Even brief hypotony must be avoided. Any remaining steps, such as an anterior vitrectomy, are also better left for when the hemorrhage has stabilized or resolved. An attempted vitrectomy by an anterior segment surgeon risks iatrogenic damage to the retina and may allow extension of the hemorrhage.

Pre-placed sutures, recommended in high-risk patients, can be rapidly tied in response to a developing SCH, functioning as an important safeguard. As we know, wounds in standard phaco surgery are often self-sealing, as long as instruments have been removed from each (well-constructed) wound. But you should still consider safety sutures when a larger-than-normal incision is required, particularly in patients with risk factors for SCH.

Once you've sealed the surgical incisions, the globe will pressurize, counteracting the expansile force exerted by progressive suprachoroidal bleeding, and the hemorrhage will be tamponaded.

Some surgeons will intraoperatively drain an SCH via scleral cutdown. But this is typically not necessary unless you're unable to close the surgical wounds and pressurize the globe. Furthermore, the skills to safely and rapidly create scleral windows aren't commonly held among anterior segment surgeons. If you are unable to close the surgical wounds and pressurize the

Table 2. Dos and Don'ts for Managing an Intraoperative Suprachoroidal Hemorrhage

DO	DON'T
• Secure any non-self-sealing incisions to pressurize the globe • Instruct the anesthesia provider to administer medications for control of: —Blood pressure —Pain • Place the patient in the reverse Trendelenburg position • Consider administering IV mannitol	• Attempt additional steps such as nuclear fragment removal, IOL placement or viscoelastic removal • Place any undue pressure on the globe (i.e. tight speculum)

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

Use of corticosteroids may result in posterior subcapsular cataract formation.

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.

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.

Use 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.

In clinical trials, the most common adverse drug reactions were eye pain (1%) and posterior capsular opacification (1%). These reactions may have been the consequence of the surgical procedure.

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Intraocular Pressure (IOP) Increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as 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—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—Use of 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—The preservative in INVELTYS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of INVELTYS and may be reinserted 15 minutes following administration.

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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.

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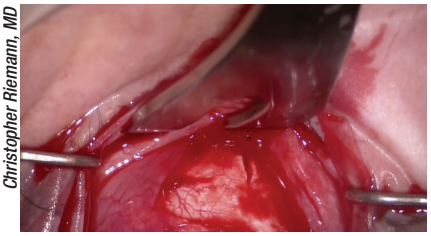
Christopher Riemann, MD

Figure 3. Creation of a scleral cutdown for drainage of a suprachoroidal hemorrhage.

globe, seek intraoperative help from a vitreoretinal colleague, if available.

Follow-up and After-care

After intraoperative tamponade of the eye, monitor your patient closely to ensure stabilization of the hemorrhage and a return to a normotensive state with a formed anterior chamber. Postop topical steroids and cylcoplegia are important for controlling pain and inflammation. Treatment of IOP may also be needed. Follow the size and location of the hemorrhage with indirect ophthalmoscopy and/or B-scan ultrasound if a good view of the posterior segment is not possible.

Consider early referral to a vitreoretinal colleague for help in evaluation and management. Drainage is typically only considered for "kissing choroidals" (appositional SCHs) and is generally performed a week to 10 days after onset of the SCH, when the clotted hemorrhage begins to liquefy. The hemorrhage may be drained intraoperatively or be allowed to resorb spontaneously. In either case, retinal detachment is common because vitreous gel is frequently incarcerated in anterior segment wounds as the suprachoroidal fluids resolve.[1] Spontaneous resolution may take weeks or months.

If you had to abort cataract surgery to secure the globe when the SCH developed, you can complete any remaining steps after the hemorrhage has stabilized and the IOP and anterior chamber depth have been normalized. In some cases, you may be able to safely finish the surgery within hours to days of the original procedure. Optimal timing will vary from case to case.

Parting Advice

Even though SCH is rare, most cataract surgeons will encounter at least one during their careers. Above all, remember that rapid recognition of the problem and prompt watertight closure of all surgical wounds can prevent a catastrophic outcome. REVIEW

Kavitha R. Sivaraman, MD is a partner at the Cincinnati Eye Cincinnati Eye Institute and assistant professor of ophthalmology-affiliated at the University of Cincinnati. She reports the following financial relationship: Consultant, W.L. Gore.

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Managing Suprachoroidal Hemorrhage: A Vitreoretinal Perspective

By Jonathan Tzu, MD

Although usually an intraoperative event, suprachoroidal hemorrhage can also occur postoperatively following certain glaucoma procedures. Vitreoretinal specialists are often enlisted for help in management, particularly with regard to deciding if and when to pursue drainage of the suprachoroidal blood.

Closing all surgical wounds in a watertight fashion when an intraoperative SCH occurs is critically important, not only to prevent expulsion of intraocular contents but to also maintain safe levels of IOP to mitigate damage to the eye. Many anterior segment surgeons won't have immediate access to a vitreoretinal specialist who can perform intraoperative SCH drainage, but this is often not necessary if the wounds can be rapidly secured.

However, timely referral to a vitreoretinal specialist postoperatively is important for ongoing monitoring. Postoperative management of SCH generally falls into two categories: medical management and surgical management.[1] Medical management includes cycloplegia, topical steroids and control of intraocular pressure. Smaller SCHs can resolve without significant visual consequences.

Indications for surgical management include: appositional choroidals; retinal detachment; flat anterior chamber and uncontrolled intraocular pressure. When possible, drainage is performed between 10 to 14 days after the initial surgery, when adequate time after surgery has passed to allow the blood clot to liquify so that it can be properly drained. Like the anterior segment surgeon, the vitreoretinal specialist uses serial B-scan ultrasounds to help assess the patient's progress.

Surgical management involves the creation of a posterior sclerotomy (or multiple sclerotomies) at the highest points of the SCH. These are small radial incisions made posteriorly to drain the liquified hemorrhage. Large clots can be removed with the assistance of a cyclodialysis spatula. IOP is most easily maintained with an anterior chamber infusion, as opposed to a pars plana infusion line. Vitrectomy can be done at the same time or in a delayed fashion if there is a concurrent retinal detachment.[2] Perfluorocarbon and silicone oil are often used to create space and to supply internal tamponade in these cases.

Reported outcomes for appositional SCH are generally poor. Limited vision and phthisis are not uncommon. Many cases involve expulsed intraocular contents, retinal detachments, periods of elevated IOP and other factors that will limit the visual outcome.[3] Proper and timely management will help mitigate some of the losses in these tough cases.

Dr. Tzu is a partner at Retina and Vitreous of Texas in Houston, Texas. He reports no financial disclosures related to this article.

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An iPhone for an Eye Doctor

Experts discuss the iPhone 11, evaluate its newest features and talk about the future of smartphone technology.

Christine Leonard, Associate Editor

The iPhone 11 series was released on September 20, touting longer battery life, faster processing speeds and a dual- and triple-camera set up. Apple assures customers, "It just got a whole lot harder to take a bad photo."[1]

The low-end 11 model is available in six different colors: black; green; yellow; purple; red and white. The premium models—the Pro and Pro Max—come in gold, space gray, silver, and midnight green.

In this article, experts weigh in on the features of the new iPhone 11 and how they stack up against previous models.

iPhone 11 Pro and Pro Max come in several different colors and feature a triple-camera system.

At First Sight

Doctors will appreciate the iPhone 11's robust battery life and enhanced durability, says Ken Lord, MD, of Retina Associates of Southern Utah. "This phone also has a more powerful processor, which means certain things are going to work a little faster, like the face recognition software on the lock screen. When we're desperate for time, even tiny increments in speed help us," he says.

The iPhone 11 runs on Apple's new A13 bionic chip, which is a six-core processor that includes two performance cores (2.65 GHz each) and four energy-efficient cores. Apple hasn't disclosed the battery power of the iPhone 11, but claims the iPhone 11 will last one hour longer than the iPhone XR. The iPhone 11 Pro is said to last four hours longer than the iPhone XS and the Pro Max five hours longer than the XS Max.

"The other major upgrade with the iPhone 11 is the camera," says Rohit Krishna, MD, director of the glaucoma service and professor of ophthalmology at University of Missouri Kansas City School of Medicine. The iPhone 11 has two 12-megapixel ultra-wide and wide cameras in the rear, and one in the front. The Pro model features three rear cameras and includes a telephoto lens. Dr. Krishna says, "The new low-light technology actually gets a pretty good picture with high resolution. Cinematography is also better—this phone shoots in 4K."

A Discerning Eye

The iPhone 11 sports the same screen specs as the XR, a 6.1-inch all-screen display with Apple's liquid

Smartphone Terminology

LCD, or liquid-crystal display, is a technology that uses the light-modulating properties of liquid crystals with a backlight to produce images on a flat-panel screen. In each pixel, liquid crystals are rotated to polarize light. LCDs replaced cathode ray tube (CRT) technology.
OLED is another display technology; the acronym stands for organic light emitting diodes. Unlike LCDs that require a backlight to illuminate the screen, individual OLEDs emit their own backlights in the presence of an electric current. Because there are many backlights, as opposed to a single one, the image is sharper and more precise, and it's possible to get truer blacks and a better color contrast range. OLED screens are made from single sheets of glass and are thinner and more flexible than LCDs. They can also be made into more different shapes, have a faster response time and better viewing angles. However, they're expensive and can't be recycled, due to the electroluminescent phosphors.
AMOLED stands for Active Matrix OLED, a variation on standard OLEDs. **Super AMOLED** has integrated touch functions—the screen itself, rather than a layer on top, recognizes touch.
Apple's Retina display is based on two-point discrimination. Steve Jobs found that at 10 to 12 inches from the human eye, 300 pixels per inch is about the pixel density at which we can't discern individual pixels anymore. However, any screen could technically be "retina" by this definition if you're standing far enough away. Think of a pointillist painting.
Resolution is simply the total number of pixels on a display. It's not necessary a measure of image quality, though it's often thought of that way.
Pixel density matters more when it comes to image quality. Pixel density is given in pixels per inch (ppi); the more pixels per inch, the sharper the image. You can calculate ppi based on the resolution and the display size. The iPhone 11 has a resolution of 1,792 x 828 with a pixel density of 326 pixels per inch, the same as the iPhone XR. The iPhone 11 Pro and Pro Max have higher resolutions (2,436 x 1,125 and 2,688 x 1,242) with a pixel density of 458 ppi.
Wireless charging works through electromagnetic induction. An induction coil in the charging pad creates an oscillating electromagnetic field; a coil in the device you're charging takes power from this and converts it back into electric current to charge the battery. The **Qi wireless charging standard**, used in most major wireless charging devices, uses planar coils for inductive power as described in Faraday's law.
Octa-core processors are simply eight-core processors, often referred to as dual quad-core, since they're arranged in two groups of four cores. Typically, high performance and low performance tasks are split between the core sets, with the low-performance core running most often.
RAM, or random-access memory, can be read or changed at any time, no matter where the data is stored. In contrast, a DVD, for example, is a direct-access storage device, so reading a DVD's data depends on rotation speed and the data's physical location in the DVD. Apple hasn't disclosed the size of the iPhone 11 series RAM officially, but Chinese regulatory agency TENNA reports that the iPhone 11 models have 4 GB of RAM, which is pretty good for a flagship phone.

—CL

retina HD screen (a type of LCD screen). The Pro and Pro Max versions of the iPhone 11 have 5.8-inch and 6.5-inch screens, respectively, with OLED (organic light emitting diode) displays. OLED has certain advantages over LCD in terms of design and function that will probably make it the technology of choice in future screen-based technologies. (For more detailed explanations of certain terms used in this article, see the "Smartphone Terminology" sidebar, above) Dr. Lord says OLED displays provide the highest quality images yet, with better color contrast and truer blacks.

But when it comes to pixel density and resolution, Dr. Lord says the upgrades in resolution we're seeing (or not seeing, rather) don't make a huge difference. "The resolution on a retina screen is actually better than what the human eye can discern," says Dr. Lord. That's due to two-point discrimination. He explains, "Ten years ago, you could see the individual pixels on CRT or LCD screens. Now resolutions are so high that we can't discern individual pixels. It looks great, but you can add as much resolution as you want, and we're not going to be able to tell."

The iPhone 11 has a resolution of 1,792 x 828 with a pixel density of 326 pixels per inch, the same as the iPhone XR. The iPhone 11 Pro and Pro Max have higher resolutions, each with a pixel density of 458 ppi. The major display upgrade between the 11 and the Pro or Pro Max would be screen type—OLED over LCD—more than pixel density.

Stereoscopic Vision

The iPhone 11's dual-camera technology mimics the human eye in more ways than one. The ultrawide and widefield lenses aid in depth perception and focusing. Additionally, like rod and cone cells, one lens captures monochrome data while the other captures RGB data. The company says that com-

bining the contrast and color data from both lenses yields a more vivid, detailed image—especially in low light, because the dual input allows for greater light capture without extended exposure time.

The iPhone 11 Pro and Pro Max have a triple-camera system: the 120-degree field-of-view ultra-widefield lens; the wide lens; and an additional 52-mm focal length telephoto lens with 2x optical zoom. The telephoto lens combined with the other two allows for an expanded field of view with a 4x optical zoom range. Machine learning and algorithms improve highlights and details, as well as recognize faces to relight them.

Connectivity

The iPhone 11 comes with a USB Type-A cable, so if your MacBook is from 2015 or later, you'll need an adapter in order to work with the laptop's USB Type-C port. The iPhone 11 Pro and Pro Max have USB Type-C connectors. USB Type-C is becoming the new connection standard for data transfer and device charging; it's much smaller than USB Types-A and -B and can therefore be used on slimmer, lighter devices. You also won't have to flip a USB Type-C connector over at least three times to fit it into the port.

Wireless charging and fast-charge capabilities are both possible for the iPhone 11 with a wireless charging pad or an 18-W adapter, sold separately. However, "there's no reverse charging," says Vinay Shah, MD, of Dean McGee Eye Institute at the University of Oklahoma in Oklahoma City. "I was hoping for that." Reverse charging allows you to use your phone to charge another phone with reverse charging capabilities. It's a slow, low-power process meant more for sustaining a battery that's at the dreaded 5-percent level.

Storage Capacity

The iPhone 11 starts at $699 for 64 GB of storage. You can upgrade to 128 GB ($749) or 256 GB ($849). The iPhone 11 Pro has greater storage capacity—up to 512 GB for $1,449. As with previous models of the iPhone, there are no expandable memory capabilities.

For Dr. Krishna, the limited 64 GB capacity of the lower-end iPhone 11 isn't a big deal. "I ultimately see storage capacity going away since everything is moving to the cloud," he says. "I've moved over to the cloud this year. I don't even use my local hard drive anymore on my Mac." However, users who haven't moved to the cloud or prefer local storage may find the 64-GB capacity restrictive, especially for storing high-quality photos and 4K videos.

For comparison, the latest Samsung phone released in September (though not yet available in the United States), is the Galaxy A90 5G. This 5G smartphone features a 48-megapixel rear camera, a 32-megapixel front camera and a Super AMOLED 6.7-inch display. It has 6 or 8 GB of RAM and an octa-core chip with processing speeds of 2.84 GHz, 2.42 GHz and 1.8 GHz. The phone comes with 128 GB of internal storage and can also accommodate a microSD card up to 512 GB for a total of 640 GB of storage capacity. It's one of the cheaper 5G phones available, starting around $827.

Artificial Intelligence

Dr. Shah says the iPhone 11 Pro is better-suited for artificial intelligence and machine learning than previous models because of its processing power. "This may be the leap they're looking for in this phone," he says. Apple's A13 bionic chip in the iPhone 11 Pro has an octa-core processor with a machine-learning focus, according to Apple. Machine learning and artificial intelligence play a major role in digital camera technology like image stabilization and facial recognition, but they have many more potential applications.

"The big thing we talk about in ophthalmology with machine learning is diagnosis and fundus imaging," says Dr. Shah. "The only FDA-approved artificial intelligence system for ophthalmology is the IDx-DR system, which uses AI to diagnose

The iPhone 11 Pro has a triple-camera system.

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diabetic retinopathy. In theory, a patient could use a phone to take fundus pictures, apply pattern recognition and AI, compare it to other pictures in a depository and then use the phone's processor to self-diagnose diabetic retinopathy and other ophthalmologic disorders; this would be especially useful in rural settings or developing countries where retina specialists or general ophthalmologists aren't readily available."

No 5G for iPhone

The 5G wireless transmission standard is coming—and it's coming fast. 5G networks are exponentially faster than previous transmission standards like 4G and 3G networks. This means faster upload and download speeds and greater signal strength.

Dr. Krishna says next year's iPhone will supposedly have a 5G chip. "There's going to be a lot of cool things with 5G," Dr. Krishna says. "It all has to do with speed. It wouldn't surprise me to see products using more artificial intelligence or augmented reality—maybe even holograms.

"For ophthalmologists, getting 5G will be a huge upgrade," he continues. "I think you'll see it permeate ophthalmology a bit more. For the most part, we haven't been too involved with augmented reality and virtual reality, but I can see more integration with those activities if we had 5G speeds." Augmented reality can be used for planning surgeries, and a surgeon wearing a headset can see digital information directly projected over the visual during procedures.

A Clinical Multi-Tool

Speed and long-lasting battery life aren't just useful for streaming movies. Though many of the fun features of iPhone 11 will be more applicable to your personal life than to work, a good phone is now an important tool to have. Here's a look at some of the ways smartphones have reshaped the clinic:

• ***As your on-call bag***. "You have EHRs, a blue light, a flashlight, color plates and fixation targets all on your phone now," says Dr. Shah. "We used to have a toy or something to distract a child, but now it's your phone—every kid loves a phone. If you have an interesting fixation target on your phone, that's a very powerful tool to grab the child's attention so you can examine them."

• ***As a pager.*** Dr. Shah says that 10 years ago, he used to carry around a pager, a personal digital assistant and a flashlight. "All of that is now my iPhone," he says.

• ***As a reference.*** You can download the Wills Eye Manual to your phone for convenient reference in the clinic or on call. Dr. Shah says Google is another resource that may offer a rare diagnosis you hadn't thought of—though perhaps don't tell your patients you're Googling their conditions.

• ***For a second opinion***. "If you want to get a second opinion on the fly as you're in the clinic, you can take a picture of some test results and send it to your friend," says Dr. Shah. "But be mindful of HIPAA—text messages aren't HIPAA-compliant, but as long as no patient information is visible, it should be okay to send a generic picture for getting a second opinion. You should use a secured email service instead of text messaging for sending sensitive information.

"Another great resource is forums," continues Dr. Shah. "The cornea people have their forums and the glaucoma people have theirs. You can post pictures on subspecialty forums and get multiple opinions from all over the world—that's a great asset."

• ***For office work.*** Dr. Shah says your phone is your scanner, your Rolodex, your file storage and your meeting place—with video-conferencing apps, you can hold meetings anywhere.

Working From Phone

You can access your EHR remotely from your phone and even view your patient images, since most major imaging devices now have mobile portals. Dr. Shah adds that with the correct apps, you can also do coding.

Being able to look up patient medical records from your phone while on call is convenient, but Dr. Krishna says to make sure you're using an app

Fundus Photography with iPhone

By attaching an adapter to your smartphone, you can take a fundus or slit lamp photograph. Ken Lord, MD, of Retina Associates of Southern Utah, notes that any new adapters will need to accommodate the additional lenses and different lens positions on the new iPhone 11 series.

There are two main types of smartphone adapters: One attaches the phone to a slit lamp microscope or other imaging device that uses microscope lens capabilities. Images are sent to the phone camera. The other type is for indirect ophthalmoscopy. "You hold an indirect lens and use the phone's camera flashlight to power the light on the image you're trying to achieve," Dr. Lord explains.

"Some people have gotten really good at it," says Rohit Krishna, MD, director of the glaucoma service and professor of ophthalmology at the University of Missouri Kansas City School of Medicine. "They've published pictures." The portability and low cost of smartphone-based imaging makes it more than just an opportunity for a photographic hobby. Low-cost fundus imaging with smartphones in developing countries can have a major positive impact on patient care, according to a 2017 study.[1]

1. Ademola-Popoola DS, Olatunji VA. Retinal imaging with smartphone. Niger J Clin Pract 2017;20:3:341-5.

like Citrix, which handles workplace encryption and secure access.

"Right now, our phones are just a window to a desktop system," says Dr. Lord. "If I want to log into my EHR to look up my patient, it's not on some dedicated app that's intuitive and user-friendly. Some EHRs have been specifically designed for iPads, but mine was not."

Patient portals are also shifting to mobile devices, since more and more people are doing things on their phones, notes Dr. Lord. He says that "companies are trying to improve mobile patient portal interfaces, but there's still a long way to go." Having an easy-to-use patient portal for mobile devices makes it more likely that patients will use the portals.

Should You Get the New iPhone?

Ultimately, tech specs won't be the only factors that influence your choice of smartphone—Apple's latest and greatest is appealing for more reasons than its 2.65-GHz processors or its 2,000,000:1 contrast ratio. Many will purchase the iPhone 11 out of brand loyalty or a desire to have the newest Apple product. Others will choose it just because it looks like a really cool phone.

One caveat: Dr. Lord notes that a cool phone won't make you a better doctor, though a faster one might help you be more efficient at work.

Dr. Krishna says that if you're a photography buff or if you find your battery is always running out and don't carry a spare, upgrading to the iPhone 11 could be a good move. The greater processing power of the premium models is also a draw, he says.

From the XR to the 11, there's not a huge leap besides the improved camera technology. The Pro and Pro Max with their triple-camera systems, OLED display technology and octa-core processors are a step up from previous iPhone models and carry the aesthetic appeal of the Apple brand, but many other phones on the market also have OLED displays, multiple camera lenses and octa-core chips. However, sometimes minor upgrades in phones are good. Dr. Shah points out that too many differences in a phone upgrade can be difficult to adjust to.

The room for improvement may be diminishing as well. "The iPhone 11 is a better phone than the iPhone 10," says Dr. Lord. "But is the 'better' offering us more functionality over previous models?" He says we've plateaued. Moore's Law forecasted exponential growth in computing power—and for a long time, technological innovations followed along this steep growth trajectory: We had floppy disks and 5-MB hard drives not so long ago, and today we have phones that can match a standard laptop for computing power. Now the growth seems to be slowing.

"It's like driving a car," continues Dr. Lord. "The technology behind cars has been the same for 80 years: four wheels, a steering wheel, and you drive down the road. Now they're faster and you have cruise control, but the concept's the same. Cars are also getting better and better, but a car today accomplishes the same thing as it did 20 or 40 years ago."

This is the case for almost all smartphones on the market. And like cars, the race for innovation among smartphone manufacturers seems centered on adding more of everything—more megapixels, more camera lenses, the latest display technology. But as these experts point out, "more" doesn't always mean discernibly better.

Drs. Lord, Krishna and Shah are the developers of and have financial interests in ophthalmic reference apps called EyeHandbook and EyePatient.

1. iPhone 11. Accessed Oct 3 2019. apple.com/iphone-11.

Cross-linking: Tackling The Big Questions

Christopher Kent, Senior Editor

The procedure continues to evolve as new approaches are proposed and existing ideas are refined.

Like anti-VEGF injections, cross-linking offers hope to patients who previously had little. And, like anti-VEGF treatments, cross-linking is in a state of rapid evolution. Physicians and researchers around the world are working to improve the procedure so it can produce the best results for the most patients, with the least risk and discomfort.

Here, surgeons with extensive cross-linking experience share the latest ideas and data relating to a host of cross-linking issues.

Leaving the Epithelium On

It's no secret that having to remove the epithelium (to ensure that sufficient riboflavin reaches the stroma) is the biggest downside of epi-off cross-linking. "Most of the risks connected to the procedure—for example, poor healing, infection and haze—are related to removing the epithelium," says Kathryn M. Hatch, MD, director of the refractive surgery service at Massachusetts Eye & Ear and an assistant professor of ophthalmology at Harvard Medical School. (Dr. Hatch was an investigator in the CXLUSA study from 2011 to 2016, and says she currently treats 20 to 30 eyes a month using the FDA-approved Avedro system.) "The issue has been getting epi-on to work as well as epi-off."

To eliminate the need for epithelial removal, several methods for enhancing the passage of the riboflavin through the epithelium have been developed. Some succeeded in getting the riboflavin past the epithelium, but drawbacks became evident, including a regression of the cross-linking benefits between one and two years postoperatively.[1,2]

Recently, however, several promising new approaches to performing cross-linking without removing the epithelium have emerged. (In addition to the epi-on systems profiled below, Avedro is setting up a clinical trial of its own epi-on cross-linking system. You can find more information about that online at ClinicalTrials.gov, identifier: NCT03442751.)

The CXLUSA system

CXLUSA (mentioned earlier) is a group of American ophthalmologists testing a new approach to epi-on cross-linking. They're using technology owned by a company called CXL Ophthalmics to perform the new procedure, and some results of their studies have already been published.[3,4]

Here's how their approach works: After instillation of proparacaine at the slit lamp, the epithelium is gently

brushed with a specially designed sterile sponge soaked with proparacaine to increase epithelial permeability. Then, with the patient in a supine position, another specially designed sponge is placed against the cornea and saturated with a proprietary riboflavin solution. After 10 to 15 minutes the cornea is evaluated to make sure sufficient riboflavin has reached the stroma; if necessary, additional time is spent. Researchers report that most eyes are saturated in 10 to 15 minutes; all were saturated by 30 minutes.

At this point the cornea is rinsed with BSS to remove excess riboflavin. The eye is then exposed to UV light (4 mW/cm^2) for 30 minutes, using a proprietary light device that cycles the light on and off, allowing the cornea to re-oxygenate during the dark phase. No additional riboflavin is added during the light exposure.

One of the published studies describes the results of this treatment on 512 keratoconic eyes and 80 post-LASIK ectasia eyes at Woolfson Eye Institute in Atlanta.[3] Findings included: No progression (defined as an increase in K-max of more than 1 D and loss of more than one line of CDVA) was observed in any eyes after two years. The epithelium was intact on the first postoperative day, except for rare cases, in which a small, central, epithelial defect was present. Postoperative pain lasted only one day, and visual acuity returned to preoperative levels in two to three days. It produced a significant improvement in UDVA, CDVA, K-max, coma and higher-order aberrations; in fact, the researchers report that the positive effects of this approach equaled or exceeded those of the same measures following the FDA-approved epi-off protocol. In addition, the amount of energy delivered during the procedure was one-third less than that used in the Dresden protocol (3.6 J/cm^2 vs. 5.4 J/cm^2). Perhaps most important, the benefits didn't regress by two years postoperatively, as they did with previous epi-on protocols.

R. Doyle Stulting, MD, PhD, director of the Stulting Research Center at Woolfson Eye Institute and professor of ophthalmology, emeritus at Emory University in Atlanta, is a member of the CXLUSA group. (Dr. Stulting performed the first cross-linking procedure in the United States, in January, 2008, as part of an FDA trial that eventually led to approval of epi-off CXL.) "Some physicians are skeptical of this new approach," he notes. "Since CXL Ophthalmics has not allowed widespread use of its patented technology, others haven't been able to see the outcomes themselves. In addition, many ophthalmologists are aware that previous epi-on techniques failed to produce lasting results. Mistakenly, they believe that all epi-on crosslinking is the same. This uses a different riboflavin formulation, and the way it's applied is unique. Also, alternative methods may not have allowed sufficient dark-phase time for diffusion of oxygen into the stroma.

"In any case," he says, "the clinical trial data indicates that our approach really does work."

"Custom Fast Cross-linking"

Robert L. Epstein, MD, director of the Center for Corrective Eye Surgery in McHenry, Illinois, has worked with a group in Italy that's developing a new epi-on protocol pioneered by Ciro Caruso, MD. It differs from the Dresden epi-off protocol in a number of ways, including a riboflavin formulation that incorporates vitamin E to help it penetrate the epithelium. They refer to their method as "custom fast cross-linking," or cfCXL.

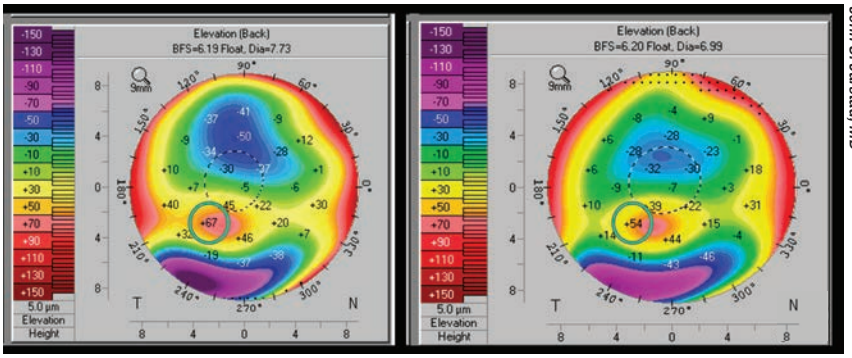
According to one of their published studies,[5] this protocol involves no epithelial disruption, 15 minutes of corneal presoaking with a riboflavin-vitamin E solution, and a 370-µm UV beam centered on the most highly

curved corneal region. The report notes that the UV beam fluence, total energy and exposure time are all significantly smaller than in the Dresden protocol. This seven-year study, using this method on 81 eyes of 81 patients, found that cylinder was reduced by 26.1 percent at one month postoperatively and 44.2 percent at seven years; best corrected visual acuity improved in 54.3 percent of patients at one month and 82.7 percent at seven years. At year seven, 98.8 percent of patients had no increase in K-max. Average corneal apex flattening was -2.79 ±1.7 D at one month postop and -4 ±2.40 D at seven years.

Dr. Epstein explains that several factors set this treatment apart. "The basic idea is that you want to adjust the energy according to the corneal thickness—i.e., use less energy on a thinner cornea," he says. "You don't want to exceed the level that's toxic to the endothelium." He notes that cfCXL takes several factors into account that change as corneal thickness changes, including how quickly the riboflavin disappears during treatment. (A paper in *Cornea* explains the mathematics of this.[6])

"Keep in mind that our protocol washes the riboflavin off the corneal surface before UV exposure," he adds. "That means that less fluence is needed than in the Dresden protocol, because adding riboflavin and leaving it on the cornea in that protocol acts as a barrier, creating a need for a higher UV light energy level. It also adds to the variability of the result. Washing the riboflavin off makes the outcome more accurate and reproducible."

Comparing the new cfCXL and CXLUSA epi-on protocols, Dr. Epstein notes several differences. "For one thing, they rub the cornea for 15 seconds with a sponge soaked with their solution," he says. "They reported that about 5 percent of their patients had small epithelial defects afterwards.[3] Our system doesn't involve any mechanical disruption of the cornea; it's completely nondestructive. Another difference is that we required documentation of progression before treatment. They did not. In our study, patients were followed for six months before treatment; those that didn't show progression were excluded. I believe the average preoperative increase in K-max was 2 D among those accepted into the study, so these were very progressive cases."



John S. Jarstad, MD

Results of six months of oral riboflavin and sunlight exposure. Visual distortion resolved; BSCVA went from 20/30 before treatment to 20/20 after. Posterior float was reduced from +67 to +54; K-max dropped from 51.8 D to 51.2 D; and inferior steepening was reduced.

Treating With Oral Riboflavin

Most variations on the cross-linking procedure center around finding better ways to get the riboflavin into the corneal tissue. Recently, a novel approach was suggested by John S. Jarstad, MD, FAAO, associate professor of clinical ophthalmology and director of cataract and refractive surgery at the University of Missouri School of Medicine. His approach involves the use of an oral riboflavin supplement and taking advantage of the UV light that's readily available in sunlight. As unlikely as it may sound, the clinical data so far suggests that this approach may be effective.

"About eight years ago we were one of the FDA sites for the Phase I trial of cross-linking," Dr. Jarstad explains. "A patient came in with post-LASIK ectasia, and we thought she'd be a great candidate for cross-linking. At the time, the cost was $3,500 per eye and it wasn't covered by insurance. I explained to her why she needed it, and what would be involved—scraping the cornea and so forth. She started crying and asked if we didn't have something cheaper and less painful."

He came up with the idea of seeing what would happen if she simply took riboflavin and spent time in the sun. He suggested 50 mg of riboflavin a day and 15 minutes in the sun. "She came back six months later, and to my surprise she had exactly the same results we were achieving with the commercial treatment," he says. "However, she admitted that instead of taking 50 mg of riboflavin, she'd been taking 500 mg a day for six months."

After seeing that result, Dr. Jarstad's group decided to conduct a small study. Those patients all had the same result, so they set up a clinical trial. Dr. Jarstad researched riboflavin and found that there were no reports of toxicity at any level of dosing; even children taking 400 mg/day in a migraine study had no complications. So they chose 400 mg/day as the dose, and added a control group taking 100 mg/day. "Oxygen is key to cross-linking," he notes, "so we ask our patients to walk briskly, facing the sun without wearing sunglasses between the hours of 10 a.m. and 2 p.m."

Dr. Jarstad says the results were clear. "The patients taking 400 mg or

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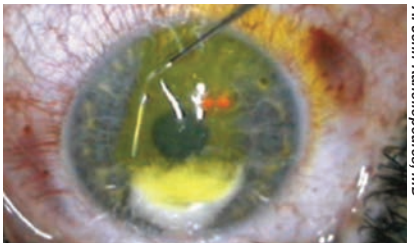
more—because some patients actually took more—got the best results," he says. "We presented that data at the international cross-linking conference in 2017 and won the award for the best research." Since then, they've opened the study to sites outside of their geographic area.

In terms of results so far, Dr. Jarstad says the protocol has worked in every single patient that has taken 400 mg or more, except for one patient who wore his hard, UV-blocking contact lenses while walking outside. "The smaller 100-mg dose seems to stabilize the keratoconus," he says. "Those patients didn't get worse, but they didn't get the same amount of improvement. The full-treatment group has had an average of 1.2 D of flattening, which is about what we were getting with the commercial trial for Avedro. Dr. Alan R. Schaeffer, at the University of Tennessee Memphis, reported that a keratoconus patient of his, a clinical dietician who read our research, took 1,500 mg per day. She suffered no ill effects and had flattening of 2.5 D.

"In terms of timing," Dr. Jarstad adds, "we've seen an effect as early as three months, but the best effect was seen after six months, which was the point at which we ended the studies. No adverse effects have been reported. Best of all, the cost is negligible. The riboflavin costs about $4 a month, and the sunlight is free." He expects to have more data within six months.

Dr. Jarstad says interested parties can find the details about the protocol on the NIH trial website: clinical trial NCT03095235. "We measure visual acuity, keratometry, corneal topography—using the refractive settings on our Pentacam topographer—and pachymetry, before the treatment and at three and six months into the treatment," he says.

Some surgeons are concerned about potential side effects of the oral riboflavin. "If you get enough concentration of riboflavin in the cornea to cross-link it, what are you doing to the skin?" Dr. Epstein asks. "I think it makes more sense to direct the riboflavin at the organ that's being treated."



A. John Kanellopoulos, MD

In one innovative approach, 0.1 mL of 0.1% riboflavin solution is infused into a femtosecond-laser-created stromal pocket.

Dr. Jarstad reiterates that no complications have been seen in his studies, or in association with large doses of riboflavin in the literature. "This protocol could be great for patients who are pregnant, as well as pediatric patients, who tend to regress after the commercial cross-linking," he says. "I don't want to discount the existing cross-linking procedure. In some cases that's the only thing that will work, because you don't always have time to wait six months for the effect. But this might turn out to be a great adjunct to other methods of cross-linking."

Using a Stromal Pocket

A. John Kanellopoulos, MD, a clinical professor of ophthalmology at NYU Medical School and medical director of the Laservision.gr Institute in Athens, Greece, explains that his group developed the idea of introducing the riboflavin into the corneal stroma via a femtosecond-laser-created cornea pocket (similar to that created for the SMILE procedure) as a way to avoid having to remove the epithelium, thus avoiding the associated disadvantages.

"We introduced this concept more than 10 years ago," he says. "If a cornea doesn't have advanced disease, the pocket can be created in a relatively simple manner. This approach has very low morbidity and rapid recovery, and, in my opinion, has a significant advantage over other epi-on approaches that administer riboflavin from the surface of the cornea inwards. If you administer the riboflavin through the corneal surface, the riboflavin left in the surface of the cornea will then act like an umbrella, blocking some of the UV light. It will reduce the efficacy of stromal cross-linking and necessitate using more energy to accomplish it.

"We've done several *ex vivo* and *in vivo* studies showing that this in-pocket epi-on cross-linking technique is very efficient and safe," Dr. Kanellopoulos adds. "However, it does require the adjunct use of a femtosecond laser, and it can only be performed safely and efficiently in corneas that are at least 400 µm thick that don't have significant apical scarring."

Dr. Kanellopoulos also notes a recent innovation. "Investigators have been collecting clinical data regarding placing a very thin allograft of tissue with Bowman's membrane into the stromal pocket," he explains. "This idea was pioneered by Gerrit Melles, MD, PhD in the Netherlands. We've tried this technique in combination with in-pocket crosslinking and we believe it might be the ultimate cornea-strengthening procedure for corneas thinner than 400 µm—those approaching the point at which a corneal transplant might be their only option."

Not all surgeons, however, are convinced that creating a stromal pocket is a good approach. "Why slice open a cornea that's already weak, when you can get the riboflavin in by much less invasive means?" Dr. Stulting asks. "The last thing you want to do is create a way for bacteria to access the corneal stroma, or create a corneal ulcer, corneal scarring or corneal perforation. I believe the risks outweigh any potential benefits."

Accelerated Cross-linking

Accelerated cross-linking refers to the idea of altering the standard pa-

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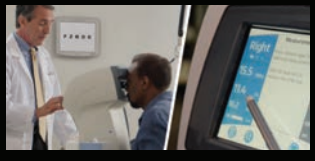

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The Issue of Cost

Many surgeons in the United States have been upset by the cost of performing Avedro's cross-linking procedure—currently the only FDA-approved option. R. Doyle Stulting, MD, PhD, director of the Stulting Research Center at Woolfson Eye Institute, points out that the actual cost of the materials needed to perform cross-linking is minimal. "Compounding the riboflavin for each patient would probably cost about $20 for both eyes," he notes. "Avedro is charging thousands of dollars per eye to get the riboflavin and the key card to turn on the light. Whatever their reasons, this is pricing the procedure out of the market for many patients."

Dr. Stulting adds that insurers aren't helping. "Ironically, Medicaid will pay for a corneal transplant, which is invasive and more costly and has the potential for many complications—not to mention the costs of altered lifestyle, missed work, and so forth," he says. "It's crazy that they'll pay for an end-stage procedure, but they won't pay for a preventative procedure that will keep patients from ever needing contact lenses or surgery.

"When a procedure is this costly, delaying payment can also have a huge financial impact on a practice," he adds. "Our practice cross-links about 20 eyes per month. If insurers delay reimbursement for six months or more, we very quickly end up with a significant financial burden. Once we discover that an insurance company is refusing to pay or delaying payment, we have to stop offering treatment to patients covered by that insurer."

This is motivating some practitioners to look for ways around the system. "I've heard of doctors purchasing a light outside the United States," Dr. Stulting says. "Then, they have the riboflavin compounded. Of course, that may put them at risk of a malpractice suit or government intervention, but everyone wants to help these patients and reduce the costs to the health-care system."

However, Kathryn M. Hatch, MD, director of the refractive surgery service at Massachusetts Eye & Ear, notes that the value of the procedure—especially compared to not treating—is significant. "I think Avedro has been the only company to spend the time and money to get approval, which is costly," she says. "And when you're talking about the value of doing a one-time procedure in a young adult to preserve their vision, the value is far more than what Avedro charges. In any case, working around the system is illegal and risky. I've seen complications in patients who've had procedures performed with non-FDA-approved devices.

"Instead, I think we should work to convince the insurance companies that this procedure has great value," she says. "We've been working on that at Massachusetts Eye & Ear, and we now have 98-percent coverage in the state. We helped convince Blue Cross/Blue Shield of Massachusetts to cover cross-linking, and that's had a huge impact on other insurers. I think almost all of the Blues in the United States are covering it now.

"Of course there are people without insurance who can't afford it, and we need to try to help them," she adds. "I treat patients who are on state insurance through Avedro's Arch program, which provides free care. Avedro supplies the drug at no charge, and I do the treatment at no charge." (According to Avedro, more than 95 percent of the commercially insured population has access to this procedure.)

To help your patients find out more about available insurance coverage, ask them to visit livingwithkeratoconus.com/is-cross-linking-right-for-me/is-cross-linking-covered-by-insurance/.

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rameters to achieve the same result more quickly—without sacrificing safety. "Accelerated crosslinking is a general term for cross-linking with any fluence greater than the classic 3 mW/cm^2 described in the original Dresden protocol," Dr. Kanellopoulos explains. "The idea is to deliver a similar amount of total cross-linking energy in less time. That reduces patient morbidity, the chance of corneal exposure to airborne microbes and the likelihood of significant corneal dehydration.

"We introduced higher-fluence, or accelerated cross-linking in 2007," he continues. "We've reported on several different techniques, beginning with our introduction of using 6 mW/cm^2 and then 10 mW/cm^2. Those include 'LASIK extra' using 30 mW/cm^2, and in-pocket crosslinking using 10 mW/cm^2."

Dr. Stulting points out that the idea of adjusting the parameters to allow a shorter procedure time has some limitations. "These modifications of the original protocol are based on the idea that the effect of a light-based chemical reaction results from the total energy delivered, rather than just the intensity," he says. "The problem is that this principle originated in reference to some specific non-biological chemical reactions; it's not meant to apply to biological events. The other problem with this concept is that oxygen is necessary for the most efficient cross-linking reaction. That places a limit on how much you can speed up the procedure, because there's a limit to the rate at which oxygen will diffuse into the cornea."

Nevertheless, Dr. Kanellopoulos says they've had success with several iterations. "Our *ex-vivo* work comparing several higher-fluence options has shown that higher fluence is relatively effective up to 30 mW/cm^2," he says. "After that, the procedure isn't significantly different from a sham procedure."

In any case, Dr. Hatch believes that customized cross-linking is the future.

"Every eye is different," she points out. "Right now in the U.S. we do the same treatment for every eye that has keratoconus. Customized treatment just makes sense."

400 µm of Tissue?

The accepted wisdom that cross-linking should only be done on corneas at least 400 µm thick has recently come into question.

Dr. Kanellopoulos notes that the 400-µm cutoff has been around for a while, and its safety has been established. "However, we've reported treatments down to almost 350 µm," he says. "Many other investigators have also established that cross-linking can be done safely at 350 µm. In fact, we're already using 350 µm as our cutoff—with the proper informed consent of the patient and family, of course."

Dr. Stulting also believes the 400 µm safety cutoff is no longer supported by the evidence. "This idea was first proposed by work in the laboratory of Theo Seiler, MD, back in 2003, and is based on experiments with rabbit corneas," he notes.[8] "More recently, Åsa Morén, MD, in Sweden, tested endothelial toxicity by directly exposing the endothelium to UV light from the endothelial side. Then he cultured the endothelial cells and looked for toxicity. He found that the threshold for cell death was orders of magnitude higher than that obtained by the original safety calculations.[9] This is important, because the whole world is avoiding treating corneas less than 400 µm thick in patients that desperately need treatment, based on data that are probably not correct."

Dr. Kanellopoulos adds that one way to lower any potential risk when treating a thinner cornea is to simply lower the amount of energy delivered. "For instance," he says, "if we're going to cross-link a cornea that's only 350 µm thick, we deliver 4.5 J of energy instead of our standard 6 J, to avoid cross-linking very deep in the cornea and reaching the endothelial level."

Iontophoresis

"Iontophoresis—using very mild electric current to draw the large riboflavin molecule from the surface into the cornea stroma through the intact epithelium—is an old idea," says Dr. Kanellopoulos. "It was pioneered in Italy, and it appears to have reasonable results, although it's not as popular as it was several years ago."

Dr. Epstein notes that published results using iontophoresis have been mixed. "A two-year study by ophthalmologist Marco Lombardo in Italy involving 34 eyes of 25 patients compared cross-linking using transepithelial cross-linking to standard cross-linking," he says.[10] "Clinically significant improvements were found in both groups, but standard cross-linking resulted in more significant corneal apex flattening. Another two-year study by Guzel Bikbova at the Ufa Eye Research Institute in Russia involving 149 eyes of 119 patients found that iontophoresis was less effective than standard cross-linking at two years, although the paper notes that both methods stopped the progression of the disease."[11]

Dr. Stulting points out that using iontophoresis for cross-linking has several drawbacks. "It's uncomfortable; it's destructive to the epithelium; and it requires extra equipment to perform," he says. "I don't know anyone who's tried it and decided to continue to do it."

Contact-lens-assisted CXL

"Contact-lens-assisted cross-linking is a brilliant idea that comes to us from Soosan Jacob, MS, FRCS, of India," Dr. Kanellopoulos explains. "The idea is to protect a cornea thinner than 400 µm from excessive UV radiance during cross-linking by adding a 50-µm thick, non-UV-absorbing contact lens to the front of the cornea. When the lens and cornea are soaked with riboflavin, the contact lens acts as a buffer, preventing cross-linking in the endothelium. I think it's a very good idea that has clinical application for corneas under the 400 µm minimal thickness."

Dr. Stulting notes that the premise—using a contact lens to increase the total thickness to 400 µm or more for safety reasons—depends on accepting the 400-µm limit as accurate. "If you don't buy the 400 µm safety limit to begin with, then you don't have to worry about using the contact lens in those eyes," he says.

Intracorneal Ring Segments

Many corneal surgeons have implanted ICRs—usually Intacs (Addition Technology, Freemont, California)—in pockets created in the peripheral cornea of ectatic eyes in order to flatten the central cornea, thus reducing myopia and astigmatism. Combining this procedure with cross-linking has been seen as a way to preserve the resulting changes. However, some surgeons have reported mixed experiences using Intacs in the cornea in combination with cross-linking.

Recently, some surgeons have begun trying a new variation on this idea, using intracorneal segments made of biological tissue rather than plastic (an idea pioneered by Soosan Jacob in India). Dr. Epstein is one of the surgeons exploring this option. "We create the rings using eye-bank corneas," he explains. "We use a special blade to cut them at whatever size and length we need, and we can make multiple segments from a single cornea.

"Using biological tissue has a number of advantages over inserting plastic segments into the cornea," he continues. "For example, if plastic segments are in the cornea and patients rub their

(Continued on page 53)

How to Ride The DMEK Boom

Sean McKinney, Senior Editor

Keep up on the latest insights and techniques needed for the fastest-growing selective corneal transplant surgery.

The number of Descemet's membrane endothelial keratoplasty procedures performed in the United States per year soared past 10,000 for the first time in 2018, representing a 41-percent increase.[1] DMEK (including a modified version called DMAEK) now accounts for 35 percent of all endothelial keratoplasty surgeries. A far cry from the 344 DMEK procedures that were completed in 2011.[2]

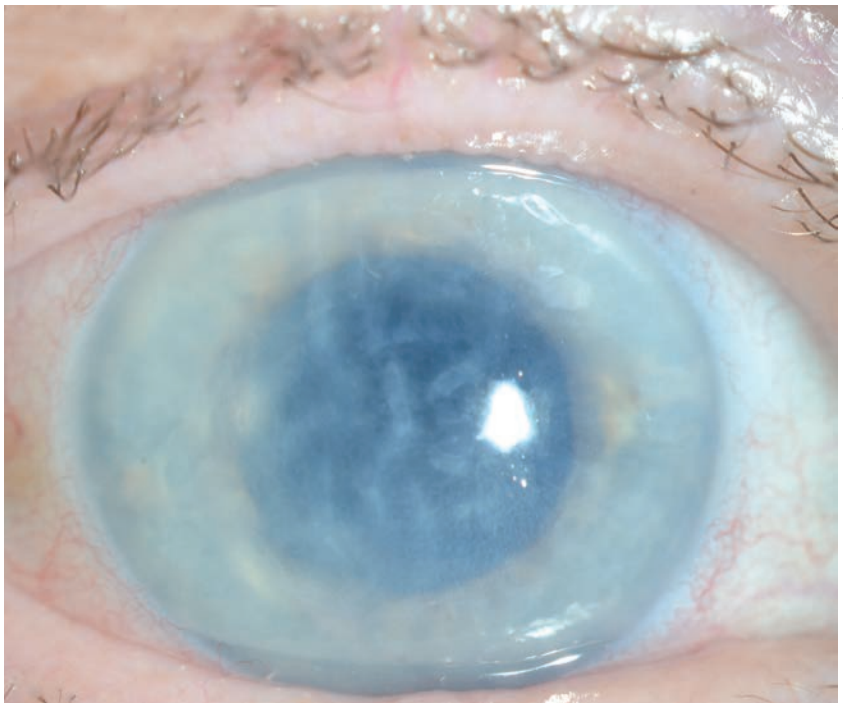
"We are at the flash point in the evolution of DMEK," says Portland, Oregon, surgeon Mark A. Terry, one of a few surgeons whose pioneering work has developed and refined this form of endothelial keratoplasty since it was introduced in 2006. "DSAEK (Descemet's stripping automated keratoplasty) has been the runaway preferred procedure and is still the leading form of endothelial keratoplasty. But DMEK started to take off in 2014, the same way DSAEK did in 2005. Now DMEK is exploding in usage.[3] The surgery will account for at least 45 percent or more of all endokeratoplasty procedures by the end of 2019. And it will just keep going up."

With numbers like these, you may be thinking of offering DMEK soon or you may be caring for patients who have undergone the procedure. Or you may be a seasoned DMEK veteran. No matter which category you're in, this article is for you. Please read along as leading DMEK surgeons review important techniques and explain how you can use them to achieve success.

Dawning of DMEK

DMEK emerged in 2009. Indications for the procedure are similar to those established for DSAEK, including endothelial dystrophies (such as Fuchs' corneal dystrophy and posterior polymorphous corneal dystrophy), pseudophakic bullous keratopathy, iridocorneal endothelial syndrome and other causes of corneal endothelial dysfunction.

"The vast majority of cases for these transplants are for Fuchs' corneal dystrophy," says Yuri McKee, MD, MS, a corneal and refractive surgeon at East Valley Ophthalmology in Mesa, Arizona. "I would strongly recommend DMEK for these patients, even if it requires referral to another surgeon." Patients who wouldn't be appropriate for most DMEK surgeries include those who have undergone complex surgeries and those who have aniridia or implanted IOLs, he notes. "You don't want any situation in which the



Gerrit Melles, MD, PhD

Figure 1. A preop slit lamp image of corneal edema from pseudophakic bullous keratopathy is shown. DMEK resolved the issue and restored a clear cornea.

DMEK transplant gets lost in the posterior vitreous," he adds.

DMEK involves the transplantation of only Descemet's membrane and endothelium, just 10 µm thick without any stromal tissue, leading to significantly better visual acuity and slightly less endothelial cell loss than DSAEK, surgeons say.

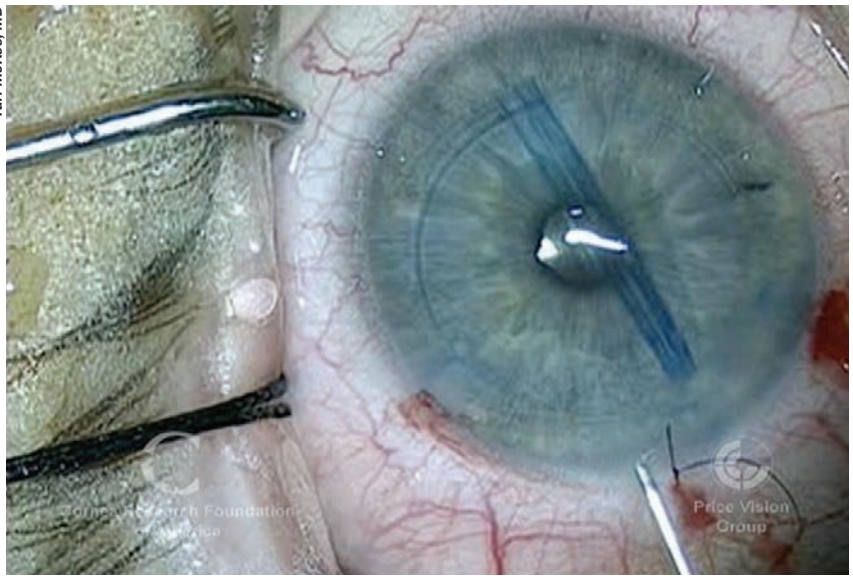
Compared to DSAEK, DMEK provides a significantly higher rate of 20/20 and 20/25 vision with comparable endothelial cell loss.[4] (Dr. McKee notes that a free digital guide to performing this procedure, "The Digital Manual of Ophthalmic Surgery and Theory of DMEK," authored by himself, Francis W. Price Jr., MD, and others, is available for free through Apple Books.)

Dr. Terry, director of Corneal Services at Legacy Devers Eye Institute in Portland, says DMEK represents the latest improvement in endokeratoplasty, resulting in improved vision, comfort and visual recovery. "The big advantage of DMEK surgery is that you're not taking out Descemet's membrane and replacing it with a thicker membrane attached to stromal tissue, as is the case in DSAEK. No matter how well DSEK and DSAEK perform, you still have the stromal interface under the DSEK and DSAEK donor tissue creating less-than-perfect surfaces."

Encouraging More Surgeons

DMEK surgeons notice that more of their colleagues are trying DMEK for the first time. The procedure, while still a challenge to learn, is easier to master than it has been in years past. Why?

Because more than 50 eye banks now offer specially processed tissue that has been pre-marked, pre-stained, pre-trephinated and pre-loaded for DMEK procedures, making the procedure faster and easier, says Dr. Terry. "This has also taken the risk out of the operating room. Now we have pre-cut, pre-stained, pre-marked and pre-loaded tissue, which is available across the United States. The process now minimizes the risk of inadvertently destroying tissue while preparing it for insertion. As a result, surgeons can feel more secure in introducing DMEK to their practices, without



Yuri McKee, MD

Figure 2. Inexperienced DMEK surgeons should avoid implanting a younger donor's graft, which creates a tight donor tissue scroll that's challenging to open. A graft from a donor age 60 or older is recommended.

losing thousands of dollars in out-of-pocket costs."

Although the DMEK learning curve remains steep, innovations like these simplify the procedure, while larger innovations loom on the horizon. (See "DSO: Clearing Vision Without a Transplant," at right.)

Updated Techniques

A number of studies show that modern DMEK is safer and more effective than in the past. For example, in a study of 80 consecutive Fuchs' cases, Dr. Terry and his colleagues used tissue prestripped by an eye bank technician, standardized DMEK techniques, a glass injector and a 20% concentration of sulfur hexafluoride (SF6) gas for prolonged tissue support.[5]

Twenty-five donors were premarked with an "S" stamp for intraoperative orientation. Surgery was performed by two experienced DMEK surgeons and two inexperienced cornea fellows. Complications were recorded, and the percent of endothelial cell loss was calculated at six months postoperatively. The results showed that five patients received an air bubble injection postoperatively (6 percent rebubble rate). Six grafts immediately failed, two of them because of excessive surgical trauma and four because of upside-down graft placement, documented by OCT.

Significantly, none of the 25 cases with an S stamp failed. Corneas cleared quickly with no clinical evidence of toxicity from the (SF6) gas bubble in the remaining corneas. The grafts experienced a mean endothelial cell loss of 27 percent at six months. As a result, Dr. Terry and his fellow researchers concluded that you can safely rely on (SF6) gas for prolonged tissue support and reduce the rebubble rate when performing DMEK. Predictably, only unrecognized upside-down grafts were the primary cause of graft failure in this series. This finding reinforced experts' advice that you can eliminate upside-down grafts by using donor tissue that has been premarked by the eye bank with an S orientation stamp.

You're Not Alone

If you're just getting started on DMEK, you won't be operating in a vacuum, like the early DMEK surgeons.

"The take-home point is that the learning curve is not nearly as difficult or fraught with hazards as it was 10 years ago," Dr. Terry says. "Back then, we were trying to determine the best way to do the surgery. Now, we have standardized the techniques in the literature being taught at multiple courses across the country. There are YouTube videos. There is so much now that, if you follow the technique and don't try to do your own thing, you can get a very rapid rise in success and minimize your risks and complications."

Gerrit Melles, MD, PhD, founder of the Netherlands Institute for Innovative Ocular Surgery, and his colleagues offer these tips for beginners:

- Overcome the learning curve and succeed as soon as possible.
- Ensure that you've selected appropriate patients.
- Choose the right diameter graft and, if possible, the right degree of graft tightness, depending on the depth of the anterior chamber.
- Flush the graft a few times outside of the eye to eliminate all the organ cultures.
- Make sure you achieve a double roll of the graft before inserting it.
- Pressurize the eye properly after surgery and leave the air-bubble in

DSO: Clearing Vision Without a Transplant

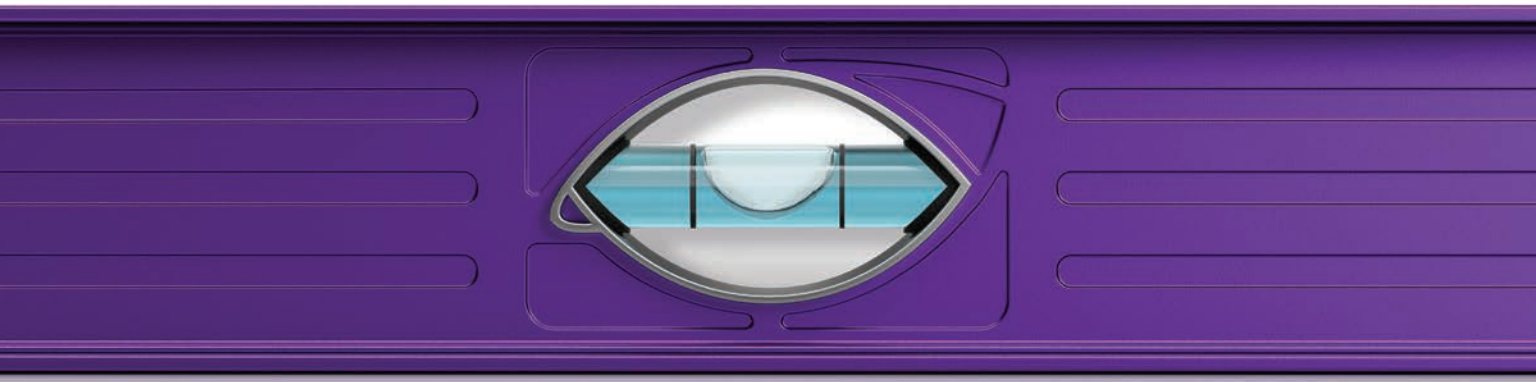
Descemet's Stripping Only is an emerging corneal procedure that holds promise, although it can only be used for Fuchs'. In DSO, the surgeon removes a 4-to-4.5-mm square central area of diseased Descemet's, but doesn't replace it with donor tissue. Instead, Rho-associated kinase (ROCK) inhibitors are applied to the stripped area, where the agents are believed to encourage the increased distribution of endothelial cells, until they cover the area of missing Descemet's membrane and facilitate a return of normal visual acuity.

"One drawback is that it takes one to two months to achieve good vision, but it works if a patient can wait that long," says Indianapolis' Francis W. Price Jr., MD, who is involved in a study of the procedure.

Dr. Price and others believe DSO will be effective if combined with Ripasudil, an approved ROCK inhibitor used to treat glaucoma and with DSO in Japan. U.S. surgeons believe Ripasudil will be approved in the United States eventually.

Netherland's DMEK expert Gerrit Melles, MD, PhD, who has experimented with DSO, says the procedure probably has limitations. "This treatment may only be possible for milder cases of Fuchs' endothelial dystrophy when there is a sufficient peripheral reservoir of cells to colonize the bare stromal area," he says. "Patients with bullous keratopathy and any other causes of limbal-to-limbal endothelial disease may not benefit from this approach because it requires some healthy endothelium to spread. The diameter may also need to always be kept small (approximately 5 mm) to ensure that the time to close the defect is not so long as to induce stromal changes by prolonged edema."

—SM



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CONTRAINDICATIONS
Contraindicated in acute superficial herpes simplex keratitis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; mycobacterial infection of the eye; fungal diseases; acute purulent untreated infections, which like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; and in those persons who have known hypersensitivity to any component of this preparation.

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

[a]**STUDY DESIGN:** The efficacy and safety of FLAREX (n=41) vs FML* (n=37) were evaluated in a randomized, double-blind clinical trial in 78 patients with ocular surface inflammation (eg, conjunctivitis, episcleritis, scleritis) in one or both eyes. In a separate randomized, double-blind clinical trial in 82 patients with ocular surface inflammation in one or both eyes, the efficacy and safety of FLAREX (n=37) vs prednisolone acetate 1.0% (n=45) were evaluated. In these studies, patients administered either FLAREX or FML*/prednisolone acetate 1.0% every 2 hours for the first 2 days and then every 4 hours thereafter, with signs and symptoms of inflammation assessed at Days 1, 3, 8, and 13. At each visit, investigators determined if symptoms in the involved eye were resolved (cured), improved, unchanged, or worsened. If a patient was rated as cured before the end of the study, steroid drops were discontinued and the patient was considered to have completed the trial.[2]

[b]Cost information based on Wholesale Acquisition Cost (WAC), 2019 data.

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CONTRAINDICATIONS
Contraindicated in acute superficial herpes simplex keratitis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; mycobacterial infection of the eye; fungal diseases; acute purulent untreated infections, which like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; and in those persons who have known hypersensitivity to any component of this preparation.

WARNINGS AND PRECAUTIONS
Topical Ophthalmic Use Only
For topical ophthalmic use only. Not for injection.

Intraocular Pressure Increase
Prolonged use may result in glaucoma, damage to the optic nerve, and defects in visual acuity and visual field. It is advisable that the intraocular pressure be checked frequently.

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Use of corticosteroids may result in cataract formation.

Delayed Healing
Topical ophthalmic corticosteroids may slow corneal wound healing. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with chronic use of topical steroids.

Viral Infections
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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.

Contamination
Do not touch dropper tip to any surface, as this may contaminate the suspension.

Contact Lens Wear
Contact lenses should be removed during instillation of FLAREX but may be reinserted after 15 minutes.

Temporarily Blurred Vision
Vision may be temporarily blurred following dosing with FLAREX. Care should be exercised in operating machinery or driving a motor vehicle.

ADVERSE REACTIONS
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Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection following suppression of host response, and perforation of the globe may occur.

Postmarketing Experience
The following reaction has been identified during postmarketing use of FLAREX in clinical practice. Because reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to FLAREX, or a combination of these factors, includes dysgeusia.

USE IN SPECIFIC POPULATIONS
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Fluorometholone has been shown to be embryocidal and teratogenic in rabbits when administered at low multiples of the human ocular dose. Fluorometholone was applied ocularly to rabbits daily on days 6-18 of gestation, and dose-related fetal loss and fetal abnormalities including cleft palate, deformed rib cage, anomalous limbs, and neural abnormalities, such as encephalocele, craniorachischisis, and spina bifida, were observed. There are no adequate and well-controlled studies of fluorometholone in pregnant women, and it is not known whether fluorometholone can cause fetal harm when administered to a pregnant woman. Fluorometholone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLAREX is administered to a nursing woman.

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Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
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Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been conducted in animals or in humans to evaluate the possibility of these effects with fluorometholone.

PATIENT COUNSELING INFORMATION
Risk of Contamination
Do not touch dropper tip to any surface, as this may contaminate the suspension.

Use with Contact Lenses
The preservative in FLAREX, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of FLAREX but may be reinserted 15 minutes after instillation.

Temporarily Blurred Vision
Patients should be advised that their vision may be temporarily blurred following dosing with FLAREX. Care should be exercised in operating machinery or driving a motor vehicle.

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References: 1. FLAREX [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2017. **2.** Leibowitz HM, Hyndiuk RA, Lindsey C, et al. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. *Ann Ophthalmol*. 1984;16(12):1110-1115. **3.** Data on file. Fort Worth, TX: Eyevance Pharmaceuticals LLC. **4.** US Department of Health and Human Services, Food and Drug Administration. *Approved drug products with therapeutic equivalence evaluations*. (Orange Book). 38th ed. Washington, DC: US Department of Health and Human Services, Food and Drug Administration; 2018.

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the eye long enough for the graft to attach.

Remaining Challenges

Among the biggest challenges facing DMEK surgeons today are graft failure, the threat of infection and complications, such as the emergent need for rebubbling, primary graft failure, rejection and late endothelial failure. "Late failure of DMEK grafts typically occurs for two reasons," says Dr. Melles. "The first is due to endothelial cell attrition and the second is rejection, though this is thankfully very uncommon."

"We routinely monitor patients with both specular microscopy and Scheimpflug imaging," notes Isabel Dapena, MD, PhD, medical director and corneal surgeon at the Netherlands Institute for Innovative Ocular Surgery in Rotterdam. "Published studies have found that changes seen in these images can potentially precede a rejection. This allows you to detect a rejection and treat the patient before the rejection takes a foothold."[6,7]

Doctors say patients affected by the beginning of rejection frequently respond promptly to topical steroid therapy. "A re-operation is not required in most cases," says Dr. Sorcha Ni Dhubhghaill, MB, PhD MRCSI (Ophth), FEBO, an anterior segment ophthalmic surgeon at University Hospital Antwerp in Belgium.

"However, if there is a secondary graft failure and inflammation, then a re-DMEK may be the best option," adds Dr. Melles.

Dr. McKee says he's had only one primary graft failure since 2015. "When I was a fellow, we ran a rejection clinic on the side of our normal clinic," he recalls. "We'd have a DSAEK rejection walk in every day."

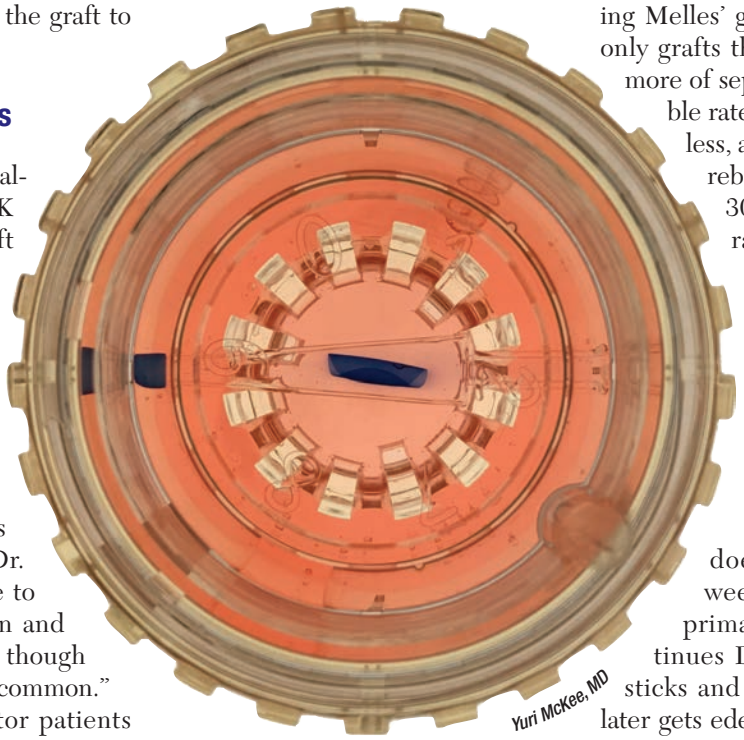

Figure 3. Pre-cut, patient-ready and pre-loaded donor tissue maximizes transplant delivery success and minimizes the financially costly risk of a surgeon destroying the tissue during preparation.

He notes that the first sign of a complication is typically corneal edema. "You have to ask yourself: Is this graft attached but not pumping fluid or is it detached and, therefore, it's obviously not going to pump fluid out of the cornea? You can use a slit lamp exam or anterior OCT to determine the graft's configuration—such as upside down, right-side up, detached or attached."[8]

Your institution may have a treatment algorithm to follow if you suspect areas of graft separation. "The decision to rebubble for areas of graft separation still remains fairly subjective," says Dr. Terry. "Some surgeons would rebubble any separated edge and have rebubble rates of 70 percent or higher. Using Melles' guideline of rebubbling only grafts that have 30 percent or more of separation yields a rebubble rate of about 10 percent or less, and the grafts that aren't rebubbled will attach up to 30 percent of the separation on their own. It's uncommon to have a primary graft failure unless the tissue is upside-down, and this is prevented by having a distinct 'S' or 'F' mark on the tissue to determine orientation.

"If the corneal edema doesn't clear within six weeks after surgery, it's a primary graft failure," continues Dr. Terry. "If the graft sticks and clears the cornea and later gets edematous, then it's a secondary graft failure. If that occurs, a rejection or some other issue should be suspected. But that's very rare with DMEK. Once it clears and attaches well and looks good by three weeks or less, you're almost always home free."

Another challenge is unfolding the graft in the eye and discovering that it's upside down.

"DMEK is like a jellyfish in water," says Dr. McKee. "It can change its configuration very quickly, turning upside down or right-side up. The grafts always curl when you unscroll. The endothelium is always on the outside of the scroll. So, when you're preparing the DMEK tissue, as some of us still do, you need to be very careful. I never begin to unfold the graft until I know it's in the correct orientation. I've had a 100-percent success rate with this, using a hand-held slit beam that shows me if the curls are coming up toward me or away from me."

When done right, the best part of DMEK is that it's almost like the

(Continued on page 50)

How to Handle Aqueous Misdirection

Christine Leonard, Associate Editor

Experts offer advice for managing this rare postoperative complication.

When managing a disease or condition, knowledge is power. But how do you manage a condition when your knowledge about its origin and mechanism is incomplete? This is the challenge of managing aqueous misdirection which, though rare, is one of the most serious complications of intraocular surgery.[1] Though experts still theorize about the condition's ultimate cause, they say that, if you're prepared for it and respond quickly, you can successfully manage cases of aqueous misdirection. In this article, physicians discuss this rare postoperative complication and share their approaches to treating it.

The Disease's Mechanism

The condition has been called several names, including ciliary block glaucoma and malignant glaucoma, derived from various theories of disease etiology, but its precise origins are unknown.

"Malignant glaucoma can be very hard to control and can seriously affect vision if not reversed quickly," says Marlene Moster, MD, professor of ophthalmology at Thomas Jefferson University School of Medicine and attending surgeon at Wills Eye Hospital in Philadelphia. She says there are several theories about the mechanism of aqueous misdirection, such as a combination of weak zonules and posterior pressure leading to axial shallowing of the anterior chamber and closure of the angle. Another is the choroidal expansion theory, which postulates that eyes prone to choroidal expansion—even a minimal expansion of 50 µm—will cause intraocular pressure to rise dramatically. Even with a peripheral iridectomy in place, the lens-iris diaphragm continues to move forward.

"What's agreed upon at this point is that aqueous misdirection is related to an abnormal relationship between the lens, vitreous and ciliary body that results in forward displacement of the lens-iris diaphragm," says Natasha Kolomeyer, MD, a glaucoma specialist at Wills.

In a healthy eye, the aqueous percolates through the vitreous to the posterior chamber and then out through the trabecular meshwork, explains Dr. Moster. "But with aqueous misdirection, the vitreous is hydrated and aqueous fluid can't easily pass anteriorly through the gel," she says. "You end up with a blockage of aqueous behind the vitreous, and this establishes a vicious cycle where the aqueous can't get out, the vitreous keeps moving everything forward and the

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intraocular pressure continues to rise.

"What we don't know is why previous glaucoma surgery makes a patient more at risk," she adds. "We only know that it changes the equilibrium of the eye. But if that's the case, why don't we see it more frequently?"

An Uncommon Complication

Studies have reported an aqueous misdirection incidence of 0.5 to 4 percent—closer to 2 percent after glaucoma surgery.[2,3] "The glaucoma service at Wills Eye Hospital sees this about five to 10 times a year," says Dr. Kolomeyer. "But we're a tertiary care center with an emergency room, so this is likely a biased sample."

Steven J. Gedde, MD, a professor of ophthalmology at the Bascom Palmer Eye Institute in Miami, agrees that it's a fairly rare complication. Citing the on-going PTVT Study, a multicenter, randomized clinical trial of 242 eyes of 242 patients undergoing primary tube versus trabeculectomy surgery (See "What We're Learning from the PTVT Study" in the October issue), he says the incidence of aqueous misdirection in the tube shunt group was 3 percent and in the trabeculectomy group, 1 percent. "That gives you an idea that this is a relatively uncommon complication," he says.

The unexpected nature and urgency of the disease are what make it a challenge to treat, says Dr. Kolomeyer. While the disease typically presents as an early postoperative condition, usually after glaucoma surgery, she notes that it can happen after other types of intraocular surgery, and in some cases it can crop up years later. "Other cases have occurred without any prior laser surgery, such as after trauma or the use of miotics," she says.

Dr. Gedde says quickly recognizing the symptoms can make a big difference in treatment outcomes. "Aqueous misdirection has a very characteristic appearance," he says. "There's axial shallowing of the anterior chamber not only peripherally, but centrally as well, due to posterior pressure."

Make note of the lens-iris position, cautions Dr. Moster. She says this may be the tip-off that aqueous misdirection is occurring. Additionally, she notes that the forward movement may push the lens dangerously close to the cornea.

Risk Factors

Patients may be anatomically predisposed to aqueous misdirection, since those who get aqueous misdirection tend to be those who already have glaucoma. Dr. Kolomeyer says hyperopia, smaller eyes, a history of peripheral anterior synechia and eyes with a propensity to have choroidal expansion or reduced vitreous conductivity are more at risk.

Dr. Gedde notes that aqueous misdirection most often occurs in patients who have chronic angle-closure glaucoma or a history of glaucoma or aqueous misdirection in one eye. "Those with a history of angle-closure tend to have more crowded anterior segments, shallower chambers, and larger lenses to begin with. Those eyes seem to be more predisposed to this complication," he says.

Diagnosing the Disease

"A shallow anterior chamber is the first thing to look for," says Dr. Kolomeyer. "But several other conditions have this feature too." Pupillary block, suprachoroidal hemorrhage and annular ciliary choroidal effusion are also accompanied by shallowing of the anterior chamber.

"It's a diagnosis of exclusion," says Dr. Gedde. "In order to diagnose aqueous misdirection or malignant glaucoma—whatever term you use—you really do need to have a patent peripheral iridectomy to rule out pupillary block."

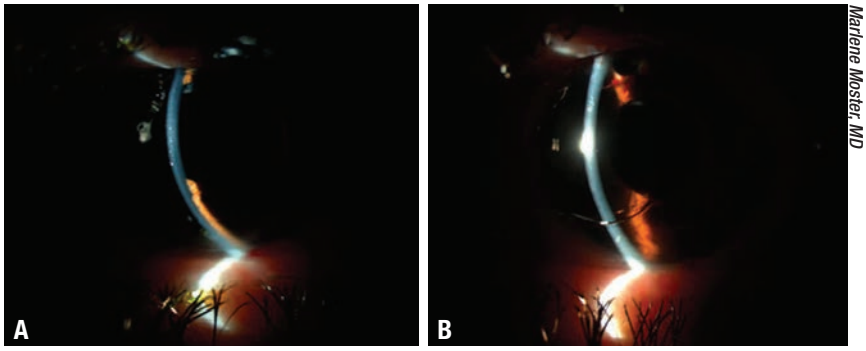
"If there's shallowing of the chamber and increased pressure due to pupillary block, an iridectomy will immediately deepen the anterior chamber," explains Dr. Moster. "Then your diagnosis is pupillary block and not malignant glaucoma."

For ruling out choroidal effusion, Dr. Gedde says you can do ultrasound biomicroscopy to check for the characteristic fluid in the suprachoroidal space under the ciliary body. An anterior segment ultrasound biomicroscopy to check for anterior rotation of the ciliary processes can also help make the diagnosis, says Dr. Moster. "Anterior rotation of the ciliary processes is very suggestive of malignant glaucoma because it indicates that there's a force pushing everything from behind," she notes.

"I generally associate aqueous misdirection with high intraocular pressure," Dr. Gedde says. "However, aqueous misdirection doesn't always present with elevated intraocular pressure. The condition can be less clear when someone has the characteristic anatomic findings of aqueous misdirection but has normal levels of

Differentiating Pupillary Block and Aqueous Misdirection

Steven J. Gedde, MD, at Bascom Palmer Eye Institute in Miami, says that pupillary block has certain features that distinguish it from aqueous misdirection. "Although the peripheral iris is displaced, there is peripheral shallowing of the anterior chamber," he says. "Usually in regular pupillary block the central anterior chamber is not as shallow. Another thing is that the lens is not shifted forward in pupillary block, and that's a marked contrast to aqueous misdirection, where the whole lens-iris diaphragm is shifted forward. So centrally, the chamber can be quite shallow as well, and that can be useful in differentiating these conditions."



Marlene Moster, MD

A 58-year old woman with a history of narrow angles, peripheral iridectomies OU, open-angle glaucoma and a prior s/p trabeculectomy done in her 30s is referred with an IOP of 44 mmHg and failed trab after routine cataract surgery elsewhere. Patient had a tube shunt, and on postop day 1, has a flat chamber touching from periphery to mid-iris (grade 2), 20/400 vision, IOP of 28 mmHg, no choroidals and patent PI. Interventions included YAG laser through the iridectomy to interrupt the anterior hyaloid, a capsulotomy and atropine. Before (Figure A), and after, with IOP decreased to 7 mmHg and a deeper anterior chamber (Figure B). The malignant glaucoma reversed without further intervention.

intraocular pressure."

A shallow anterior chamber with a normal or low intraocular pressure may suggest choroidal effusion or a leak from a surgical site, says Dr. Kolomeyer. A shallow anterior chamber with elevated pressures might be a suprachoroidal hemorrhage. "You can rule out these other diagnoses by fundus exam or B-scan," she says.

Medical Therapy

Typically, you immediately initiate treatment with medical therapy, says Dr. Gedde. There are several options for medical management of aqueous misdirection. Many are used concomitantly, as using only one class of therapy is often less effective than using them in combination.[2]

- ***Aqueous suppressants*** like beta blockers, alpha agonists and carbonic anhydrase inhibitors, are used to decrease intraocular pressure and suppress aqueous humor production. They also decrease the amount of fluid misdirected posteriorly. "Typically, atropine is given to try to dilate the pupil and shift the lens-iris diaphragm more posteriorly," Dr. Gedde adds.
- ***Osmotics*** shrink the vitreous cavity, decreasing the volume posteriorly.
- ***Steroid medications*** might be used because you have a shallow anterior chamber; you want to minimize the risk of peripheral anterior synechiae formation in that setting.
- ***Cycloplegics*** work by inhibiting the ciliary muscle contractions and causing tightening of the zonules, which moves the lens posteriorly, explains Dr. Kolomeyer. "This should break ciliovitreal adhesions and decrease the amount of posterior flow," she says.
- ***Mydriatics*** work by increasing the free surface area of the anterior hyaloid and by further promoting anterior direction of fluid.
- ***Vitreous dehydrators*** like mannitol and glycerol will allow the aqueous humor to percolate through the vitreous once again.

Dr. Kolomeyer cautions against stopping medication suddenly if you see resolution. "I taper off the medications," she says. "The last thing I would stop would be the cycloplegic agent atropine. In some cases, especially if they're recurrent, the patient might need to be on cycloplegics like atropine long-term." Dr. Kolomeyer points out that medications work in about half of cases,[4] but if the aqueous misdirection isn't resolved within three to five days, if it recurs, or if there's significant corneal decompensation related to cornea-lens touch, then laser or surgical intervention should be strongly considered.

Laser

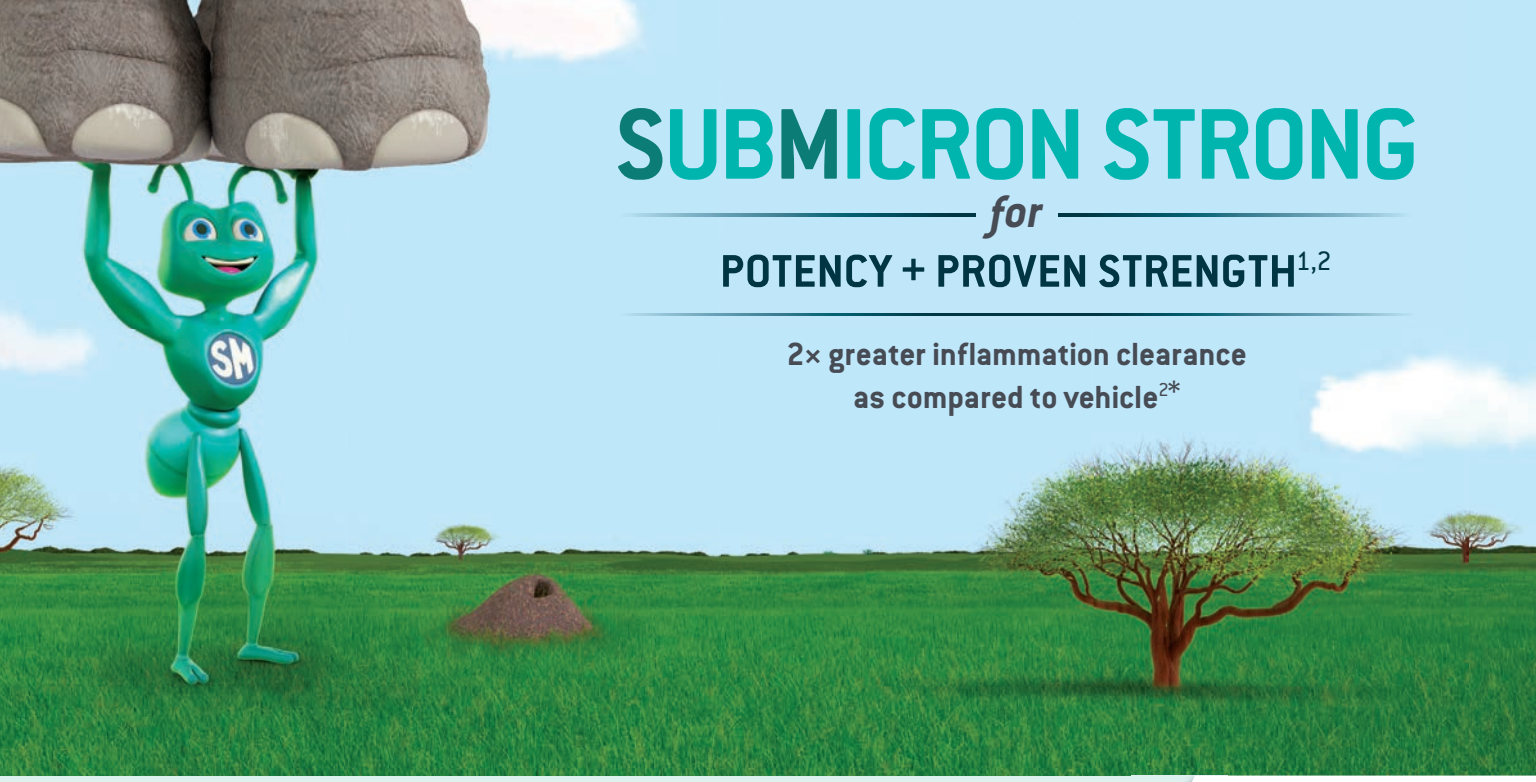
Dr. Gedde says whether laser treatment can be done depends on how much corneal edema is present. "If laser treatment can be performed, I'll usually proceed with it," he says. "It's important to do that first in a pseudophakic eye. And if you're disrupting the anterior hyaloid, it's important to do that peripheral to the intraocular lens implant."

Furthermore, "where the laser is delivered may depend on the degree of pupillary dilation—it may be in the pupil but peripheral to the optic of the lens, if that can be visualized," continues Dr. Gedde. "Otherwise, it might be done through an iridectomy if an iridectomy is present."

Dr. Moster says you can always laser through the iridectomy in a pseudophakic patient to disrupt the anterior hyaloid face, but this may not be enough. "We routinely do a YAG capsulotomy to break the vitreous face so that aqueous can percolate around the intraocular lens into the anterior chamber. For a phakic patient, we try to laser in the periphery through the surgical iridectomy if they've had a trabeculectomy. We try to break the anterior hyaloid face so the aqueous can come into the anterior chamber and exit through the normal trabecular meshwork pathway."

"We're not tip-toeing here," she emphasizes. "We really want to blow the vitreous and anterior hyaloid face apart so aqueous can start coming through. It happens immediately."

Another option is to perform diode laser cyclophotocoagulation, although this is done less frequently, says Dr.



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†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.

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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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 ≥ 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 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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Kolomeyer. Dr. Gedde adds that heat-shrinking the ciliary processes is another laser treatment that's been described, but he prefers an anterior hyaloidotomy for aqueous misdirection.

Surgery

Depending on the clinical situation, and what response you get to medical therapy and laser, patients may need surgical intervention such as an anterior vitrectomy with iridectomy, hyaloidzonulectomy or a core vitrectomy. "In my opinion, moving fairly promptly to surgical intervention if medication and laser treatment are not having any beneficial effect is important for optimizing the prognosis for these patients," Dr. Gedde explains.

For a phakic patient, oftentimes the decision will be made to remove the lens at the time of vitrectomy. "That's because the vitreoretinal surgeon can't be as aggressive when removing the anterior hyaloid, which is felt to be the area where the blockage occurs," says Dr. Gedde. "There was a theory out of the Bascom Palmer Eye Institute a number of years ago describing a pars plana vitrectomy treatment for aqueous misdirection. It had a high success rate in pseudophakic and aphakic eyes, but less so in phakic eyes unless the lens was removed at the time of the vitrectomy."

Dr. Kolomeyer agrees that the lens should usually be removed at the time of the procedure if the patient is phakic. If the patient has a history of significant glaucoma or peripheral anterior synechia, she says she would also consider putting in a pars plana tube shunt at the time of surgery to lower intraocular pressure long-term.

The goal of the procedure is to create a unicameral eye, where aqueous can flow easily from the vitreous cavity and posterior chamber into the anterior chamber, says Dr. Moster. Here are some options you can consider:

- ***Pars plana vitrectomy***. "You're cleaning out the entire anterior hyaloid face so that the blockage no longer remains," Dr. Moster says. She also suggests doing a lensectomy and capsulotomy with vitrectomy at the same time for phakic patients.

Dr. Gedde adds that you want to create a communication pathway between the vitreous cavity and the anterior chamber. "Typically that's done by passing a vitrector through the anterior hyaloid, peripheral zonules and peripheral iris," he says. "That's a critical maneuver to treat the disease."

- ***Clear corneal incision***. Dr. Moster says you can use the vitrector to go through the previously-placed iridectomy (or create one in a pseudophakic patient), go through the zonules and through the anterior hyaloid into the vitreous cavity. "You see deepening of the chamber immediately," she says. "The lens-iris diaphragm moves back into its normal position, the angle opens and the pressure comes down."

Take care in the postoperative phase. "After any surgery, I would put the patients on cycloplegic agents and anti-inflammatory medications, such as a steroid, watch their IOP and accordingly use IOP medications as well," Dr. Kolomeyer says.

Outlook

"Aqueous misdirection can't be fully resolved," says Dr. Gedde. "Unfortunately, it's one of those conditions where you may have achieved a resolution, but the condition can recur. Generally though, a restoration of normal anterior chamber anatomy is a good indicator that you've sufficiently resolved the misdirection."

Dr. Moster adds that deepening of the anterior chamber, normal intraocular pressure, an open angle on gonioscopy, lack of pain in the eye and visual acuity returning to baseline are all good indicators that the aqueous misdirection is resolved.

Experts say it's important to be vigilant—especially for high-risk eyes like those with chronic angle-closure glaucoma, or if aqueous misdirection has already developed in the fellow eye. "Make the diagnosis at the earliest possible juncture and treat promptly for a resolution that will optimize the visual prognosis," says Dr. Gedde.

Early identification of patients who may be at risk for developing aqueous misdirection may allow you to take some prophylactic measures or make intraoperative modifications, Dr. Kolomeyer adds. These might include performing a peripheral iridotomy prophylactically, depending on the patient's angle appearance, or placing them on cycloplegics after glaucoma or other intraocular surgeries. "Additionally, you may consider disrupting the anterior hyaloid or performing a vitrectomy at the same time as the planned procedure," she says.

"This is a multidisciplinary problem and requires a multidisciplinary approach," Dr. Kolomeyer continues. "Be honest with your patients about what to expect. It often goes beyond an acute episode; patients may have long-standing high intraocular pressure or cataract formation or require multiple procedures. You'll likely have involvement of the primary ophthalmologist as well as a glaucoma and retina specialist.

"I'm optimistic that further studies on this topic and improvements in imaging technology will help us learn more about aqueous misdirection and improve our treatment approaches," Dr. Kolomeyer says. REVIEW

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The Current State of Corneal Inlays

Michelle Stephenson, Contributing Editor

As corneal inlays have decreased in popularity, new treatment options have emerged.

The future for synthetic corneal inlays appears bleak. According to John Hovanesian, MD, who practices in Laguna Hills, California, it's clear that widespread market adoption of corneal inlays has not yet happened. "There were good companies and, in the case of Kamra, good products, but there has not been widespread acceptance," he says.

He adds that there are several barriers to patient adoption of corneal inlays. "As we know from experience, the two biggest barriers to LASIK are fear and cost," Dr. Hovanesian continues. "The same is true for corneal inlays. In the case of fear, I don't think patients are much more scared than they would be of LASIK, but most people don't know anyone who has a corneal inlay. Additionally, it's a device that requires patients to adapt to some degree of monovision, because it's only in one eye. That causes patient uncertainty about how well it will work for them. Most people who have not tried monovision have a negative reaction to the idea when you present it. In addition, the cost of a Kamra inlay, although it's in only one eye, is greater than the cost of LASIK. In some cases, the patient may have hyperopia or astigmatism, so he or she may have to undergo a refractive procedure as well. So, we have to overcome both fear and cost concerns with corneal inlays."

Only One Remains

Several corneal inlays have come to market in recent years, but the Kamra corneal inlay is the only one still available. Though the inlay's adoption rate by surgeons isn't anything like when PRK or LASIK were first approved, Dr. Hovanesian believes that Kamra will stick around because the company is set up to support it. "If the whole company's existence depended upon just Kamra, it would be hard to keep a company going on a small product like that," he says. "But CorneaGen has a wide variety of products that appeal to cornea specialists, and they don't need Kamra to be a blockbuster product for them. I don't think the company has any grand designs that it's going to take over the world of presbyopia correction, but I believe it's a valuable offering they will continue to make available."

Richard Lindstrom, MD, who is in practice in Minneapolis, notes that another corneal inlay has been taken off the market: the Raindrop from ReVision Optics. It's a hydrogel that was placed under a flap to cause

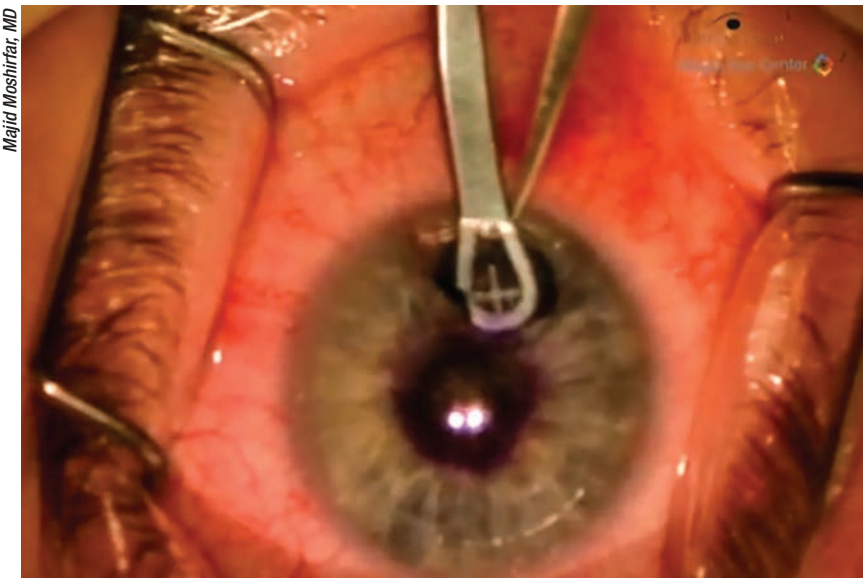
This article has no commercial sponsorship.

a central steepening of the cornea and basically create a multifocal cornea. "That particular product was removed from the market because it had some adverse outcomes, primarily related to interface haze between the hydrogel and the cornea," Dr. Lindstrom says. "Additionally, it had decentration issues. And so, while it actually did achieve FDA approval, it was pulled off the market."

Dr. Hovanesian adds that, with ReVision Optics, both the company and the technology ultimately failed, despite a respected team and a promising product. "We think the problem was the material," he says. The hydrogel material was probably not as biocompatible as another material might have been, though many patients did well. In my practice, I did about 30 of the Raindrop implants, and the vast majority of my patients did very well, but not everyone in the trial did. In the end, the FDA issued a warning saying that no more of these should be implanted. And, in fact, we've removed some of them just to prevent future problems with the implants." (The CyPass glaucoma implant from Alcon suffered the same fate. Some late complications showed up after Food and Drug Administration approval, so it was taken off the market.)

Dr. Lindstrom says the Raindrop's failure may have impacted other products. "The failure of this inlay in the marketplace obviously created a meaningful ripple effect, as far as concerns, and also created a negative perception about corneal inlays in general for the treatment of presbyopia," Dr. Lindstrom says. He notes that the Presbia company was developing a small-diameter intracorneal lens that increased refractive index and was placed in a deep pocket in the cornea. "Basically, the failure of Raindrop limited Presbia's ability to raise the capital needed to pursue its business plan," Dr. Lindstrom says. "The company still exists, but it's not active at this time. Again, I think there was a bit of a negative ripple from the failure of Raindrop, which impacted their ability to raise money."

Majid Moshirfar, MD



The last remaining approved corneal inlay, the Kamra, is inserted into a corneal pocket in the presbyopic patient's non-dominant eye.

San Diego surgeon Michael Gordon was involved in the Presbia study and says the device achieved good results. "We had very few issues with biocompatibility, but it does occur," he notes. "These issues respond very well to steroids. But we have newer IOLs and a different age population. For the 40-year-old presbyope, I think we're better off doing laser monovision. Lasers are so good now that you achieve the results you want without having to insert a foreign material into the eye."

The Kamra inlay was initially brought to the marketplace by AcuFocus, which eventually sold the inlay to SightLife Surgical/CorneaGen. "The market for the inlay is small for several reasons," says Dr. Lindstrom. "First, the presbyope, particularly the emmetropic presbyope, is highly risk-averse. Corneal inlays are usually used to treat mild to moderate presbyopia. These patients have perfect distance vision and often good intermediate vision, so very few patients are willing to accept the risk of a surgical procedure for the treatment of their presbyopia. We now better understand the market. While there are 120 million presbyopes in the United States, only a small number of them are ready to undergo surgery."

Another reason that corneal inlays have struggled is that they're in competition with monovision. "Monovision is, of course, stiff competition, so many of the patients who might have been interested in the intracorneal lens choose monovision instead," Dr. Lindstrom says. "The third reason that the inlay market is small is the negative ripple effect of seeing late complications occur in ReVision Optics' Raindrop, and concerns that these same issues could occur in other intracorneal lenses as well. To date, it hasn't been seen as frequently as with the Kamra inlay, but it has definitely dampened enthusiasm, I believe, for the whole concept of placing a synthetic inlay into the cornea for the treatment of presbyopia."

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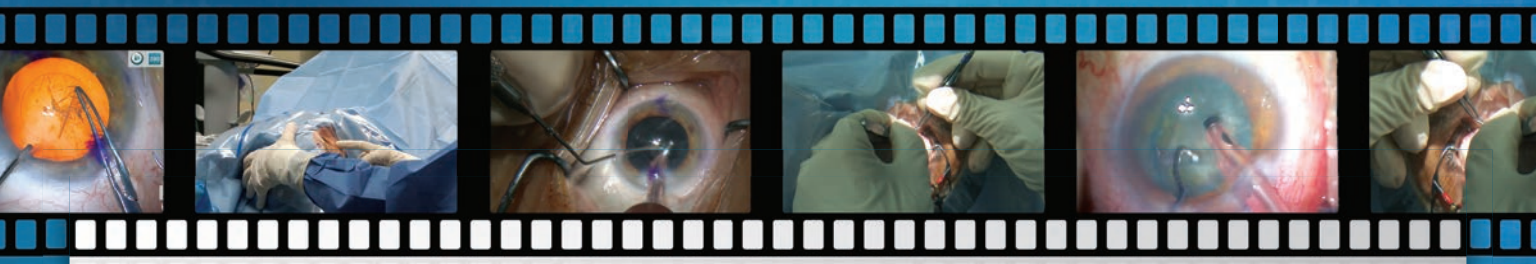

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Episode 47:

"Phacoaspiration and Trabecular Meshwork Bypass Stent Injection Techniques"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
Phacoaspiration (no ultrasound) of a nuclear cataract with IOL insertion is performed in a 64 year old patient, followed by trabecular meshwork bypass stent injection. A second example of stent injection in another patient is also shown.

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Richard J. Mackool, MD

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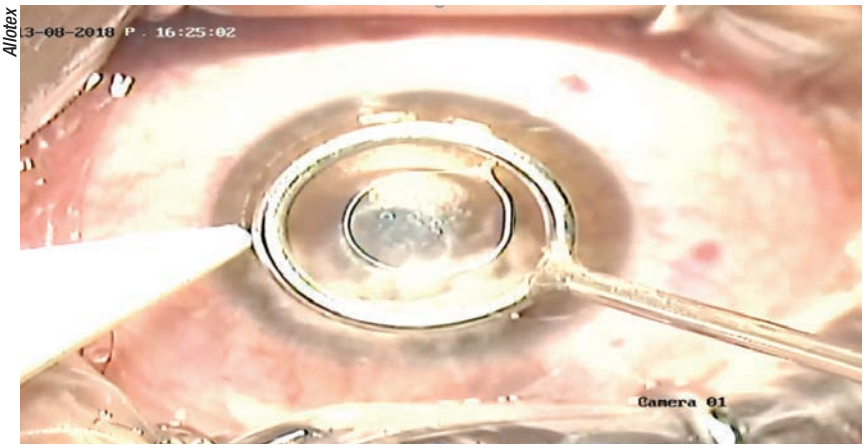
field is Allotex. Its product is similar to the Raindrop, but instead of using a synthetic material, it's using human corneal tissue. "The human tissue negates the concerns about interface haze," says Dr. Lindstrom. "They are currently pursuing an early clinical trial outside of the United States."

The Allotex TransForm lenticule is a piece of acellular cornea that's sterilized with electron beam radiation and then shaped using a laser.[1] The goal is to enhance the visual performance of the patient with a material that's 100-percent biocompatible and precisely shaped for the patient's needs. It's indicated for intrastromal implantation to provide near vision in the non-dominant eye of patients 41 to 65 years old with presbyopia and a manifest refraction spherical equivalent of +1 D to -0.75 D with less than 0.75 D of refractive cylinder, who don't require any type of correction for clear distance vision, but who do require near correction of +1.75 D to +3.50 D of reading add.



The investigational TransForm inlay from Allotex uses a piece of acellular cornea sterilized with radiation and shaped using a laser according to the patient's visual requirements.

The Future

Dr. Lindstrom is interested to see results with the Allotex inlay. "I think that will be of interest because of the obvious biocompatibility," he says. "I think there will continue to be a small following for the Kamra inlay because it does work well. I don't see that inlay failing because of complications, but it won't be a meaningful product as far as number of inlays placed. And, there is some interesting competition coming. Probably the most exciting thing coming is the pharmacologic treatment of presbyopia with eye drops."

According to Dr. Lindstrom, there are two approaches to this treatment. One is to uncross-link the human lens and increase its elasticity, which is being pursued by Novartis. Additionally, three companies, Presbyopia Therapeutics, Orasis and Allergan, are studying miotic drops. "These drops make your pupils small to basically induce small aperture optic outcomes, much like the Kamra inlay does with surgery," Dr. Lindstrom says. "These are the same drops that have been used for decades for glaucoma, so they have a long track record of safety and they are reversible. For example, if someone just wanted to see better during the day while at work but is happy to wear readers at night, he or she can use one to two drops during the workday, or if he or she is going out at night on a date and wants to read the menu without readers, he or she might use a drop just in the evening. And, depending on the drop, some might last two to four hours, while others might last six to eight hours, but they would basically be creating temporary improvement in near vision with an eye drop. Those companies' drops are all in clinical trials."

These drops have shown promise for the temporary treatment of presbyopia in trials. A study conducted in Egypt found that carbachol plus brimonidine seems to be an acceptable, safe alternative to corrective lenses and surgical procedures.[2] The prospective, double-masked, randomized, placebo-controlled clinical trial included 48 patients who were naturally emmetropic and presbyopic. All patients were between the ages of 43 and 56 years with an uncorrected distance visual acuity of at least 20/20 in both eyes without additional ocular pathology. The 30 eyes in the treatment group received a single dose of 2.25% carbachol plus 0.2% brimonidine eye drops. The control group (18 eyes) received placebo drops. Drops were given in a masked fashion in patients' nondominant eyes. Their pupil size and both near and distance visual acuities were evaluated before and after treatment at one, two, four, eight and 10 hours by a masked examiner.

The investigators reported statistically significant improvement in near visual acuity in all patients who received carbachol plus brimonidine drops. All patients in the study said they liked and would use the therapy if it was available.

Dr. Hovanesian adds that he has heard a lot of feedback about how much patients like the idea of eye drops. "Then, it becomes a question of how tolerable and expensive the drop is," he says. "But I think there will be wide acceptance of the drops."

Additionally, a couple of surgical procedures, LaserACE and VisAbil-

ity microinserts, can be performed on the sclera to enhance accommodation, either by expanding, indenting or weakening the sclera. "These are in clinical trials, but they are both surgical procedures with some invasiveness and morbidity," Dr. Lindstrom notes.

"Currently, I'm most excited about the miotic drops that can either treat presbyopia at the source by increasing natural lens elasticity or transiently improve near vision using small diameter aperture optics," Dr. Lindstrom says. "So, I think that's probably going to be the winner among the options I see coming along now. They'll probably be available in another year or two in the United States, and maybe before that outside of the United States."

Dr. Hovanesian adds that treating presbyopia is tough. "Objective data aren't always so objective," he says.

"Currently, I am most excited by the miotic drops that can either treat presbyopia at the source by increasing natural lens elasticity or transiently improve near vision using small-aperture optics."
— Richard Lindstrom, MD

"Reading vision and overcoming presbyopia are somewhat effort-dependent. When reading on the chart, it's not like there's as crisp an endpoint as there is when we're looking at a trial for macular degeneration or some other measure of visual acuity. With presbyopia, patient effort can influence the outcome, and that means that the endpoints in these studies are a little bit softer than normal visual acuity endpoints. So, a company can have really good-looking data, but the product may not work quite as well as you'd think," he cautions. REVIEW

Dr. Lindstrom has a financial interest in CorneaGen and Orasis. Dr. Gordon has a financial interest in Presbia. Dr. Hovanesian is an equity owner of CorneaGen, and was a clinical investigator for the Raindrop corneal inlay.

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(Continued from page 39)

Mark Terry, MD

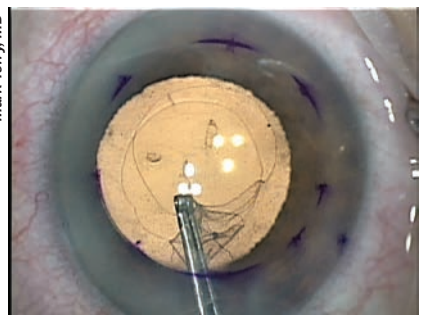

Figure 4. Straiko Twin Ring Forceps are shown stripping a 4-mm central area of a recipient patient's disease-affected Descemet's membrane during Descemet's Only Stripping (DOS) surgery. Instead of implanting donor tissue, the surgeon relies on the redistribution of the patient's endothelial cells to the central cornea to eventually restore clear vision.

graft isn't there at all. "The best way to think of DMEK is that it provides perfect anatomic replacement," says Dr. Terry. "When you have perfect anatomic replacement, visual results are comparable to that of a normal eye. There's no better service that you can provide your patients."

Dr. Terry claims no financial interests in DMEK surgical devices, but he receives royalties from Bausch + Lomb for the design of a surgical instrument used in DSAEK. Dr. Price is a consultant for Alcon, Allergan, Eyepoint, Haag-Streit, Kedrion, STAAR and Sun Ophthalmics; he's an equity owner of Interactive Medical Publishing, RxSight and Strathspey Crown. He receives grant support from Aerie. Dr. Melles is a consultant for DORC International/ Dutch Ophthalmic USA and SurgiCube International. Drs. McKee, Dapena and Dhubhghaill have no financial interest in any of the products discussed. REVIEW

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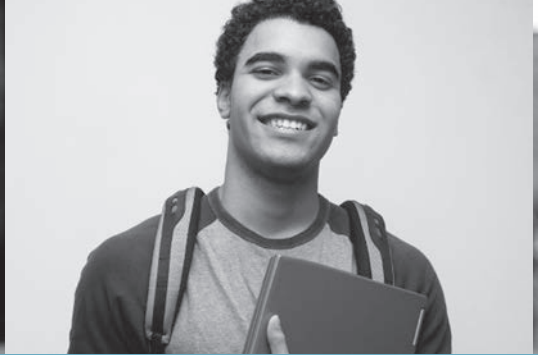


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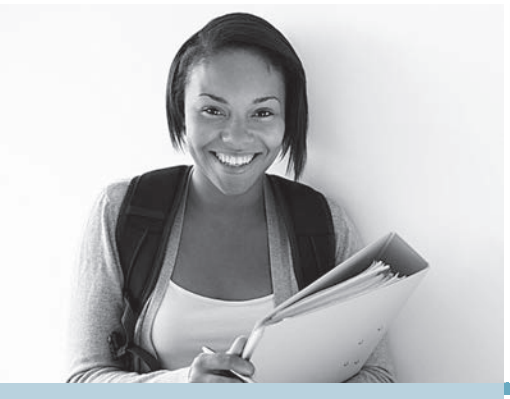

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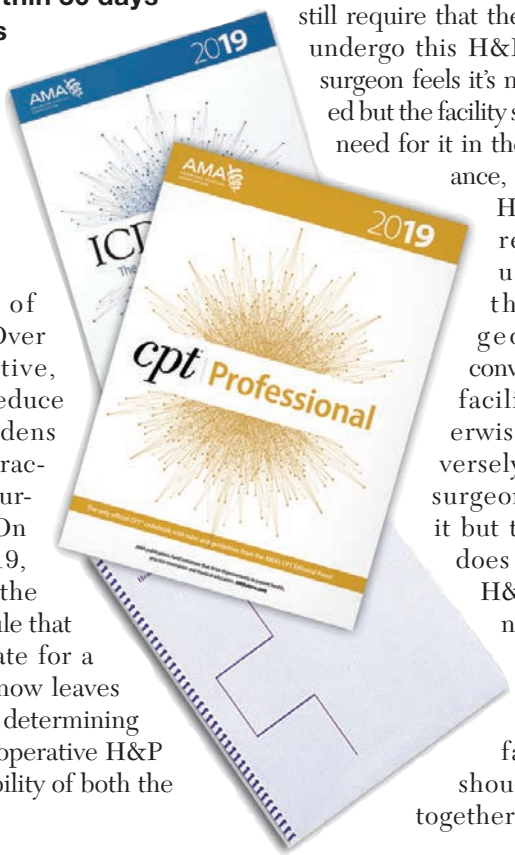
Paul M. Larson, MBA, MMSc, COMT, COE, CPC, CPMA

New Medicare Changes for ASCs

A new initiative from the Centers for Medicare and Medicaid Services will alter some requirements for surgery centers.

Q I saw that Medicare recently issued some changes regarding the need for a mandatory preoperative Comprehensive History and Physical (H&P) within 30 days before a patient is admitted for surgery at an Ambulatory Surgery Center. Is this true?

A Yes. As part of the "Patients Over Paperwork" initiative, CMS is trying to reduce the regulatory burdens on providers and practices while still ensuring patient safety. On September 30, 2019, CMS published in the Federal Register a rule that removed the mandate for a 30-day H&P. CMS now leaves the responsibility for determining the need for this preoperative H&P to the joint responsibility of both the facility and surgeon.



Q What does "joint responsibility" exactly mean in this instance?

A It means that either the surgeon or the ASC can still require that the patient undergo this H&P. If the surgeon feels it's not needed but the facility states the need for it in their guidance, then the H&P is required unless the surgeon can convince the facility otherwise. Conversely, if the surgeon wants it but the ASC does not, an H&P is still needed. Surgeons and facilities should work together for the benefit of the patient; the government will no longer mandate the H&P as a matter of course.

Therefore, if the surgeon and the ASC both agree that certain individuals don't need the H&P, then those patients can be admitted to the ASC without one.

Q Is there anything else I should know about the H&P?

A ASCs will now need to have a formal policy that identifies which patients need an H&P prior to admission. In the press release issued on September 26, 2019, CMS noted that it is "… finalizing the requirement that each ASC establish and implement a policy that identifies patients who require an H&P prior to surgery."

Q Are there any other areas parts of this rule that will help ASCs?

A One other aspect that will help ASCs is no longer needing a "Written Transfer Agreement" when

moving a patient to a hospital. That requirement is also changing for the better. The press release mentioned earlier also notes the following: [CMS is] " … removing the provisions requiring ASCs to have a written transfer agreement with a hospital … or ensuring that all physicians performing surgery in the ASC have admitting privileges in a hospital ... Instead, ASCs will be required to periodically provide the local hospital with written notice that outlines the ASC operation and patient population served by the ASC facility. All ASCs must continue to have an effective procedure for immediate transfers to a hospital for patients requiring emergency medical care beyond the capabilities of the ASC …"

Q What about the ASC's need for an annual Emergency Preparedness Program?

A CMS has reduced the need for an annual review of an ASC's Emergency Preparedness Program to a biennial review. This includes changing the annual requirement for training in this area to a biennial one. Since ASCs are inherently outpatient, they will only be required to do a testing exercise once per year instead of twice per year.

Q When do all of these regulatory changes for ASCs go into effect?

A The effective date for all of the changes is November 29, 2019, so until this date the old rule guidance remains. REVIEW

Mr. Larson is a senior consultant at the Corcoran Consulting Group. Contact him at plarson@corcorancg.com.

(Continued from page 33)

eyes, the plastic doesn't bend, but the cornea does. If enough eye rubbing occurs, the Intac can start to dislocate. That's not the case with an insert made of tissue. A second advantage is that a biologic insert can be placed inside a thinner cornea than an Intac can. And third, a biologic insert becomes part of the body when it heals. If you laser the corneal surface later, you're not going to run into plastic."

Dr. Kanellopoulos says he believes this idea is promising. "Our group has also reported using xenograft tissue in conjunction with cross-linking," he says. "We believe this may bypass some of the practical issues that come with using artificial intracorneal ring segments. Those issues include obstructing the nutrients and other materials that are transferred in the cornea, and the possibility of the rings making the cornea unstable, creating corneal melts, inviting infection and leading to other complications. Using xenograft tissue instead accomplishes the same thing with a material that's more biocompatible."

Treating a Smaller Area

One idea that's being tried with some success is cross-linking less corneal tissue outside the optical zone. This is showing promising results in both epi-off and epi-on protocols.

Dr. Epstein says this is part of the custom fast cross-linking procedure (described earlier). "We use a narrower beam of light," he explains. "In most cases of keratoconus, the localized area gets very highly curved, while areas distant from it actually become flatter. What we want to do is treat the area that's diseased, not the area that's already extra flat. By focusing the beam, we get a much greater effect, even though we're using less energy than in the past. It's because the treatment area is smaller, which strengthens the effect on the curvature."

Dr. Hatch also reports success using this approach with the epi-on protocol, in part because it requires debriding a smaller area. "I typically don't do a full 9-mm debridement of the epithelium," she explains. "Instead, I do a more limited debridement over the area of the cone. Sometimes I find that I can get a deeper cross-linking effect in that limited area, and it leads to a much faster recovery.

"You probably won't get as much flattening as if you did the Dresden protocol," she adds, "but I'm not sure every patient needs that level of cross-linking. Meanwhile, the epithelium heals in about two days, which is more like the recovery from an epi-on procedure, and you still get a very effective cross-linking treatment." REVIEW

Dr. Kanellopoulos is a consultant for Avedro and Alcon. Dr. Hatch is a consultant to Avedro and a shareholder. Drs. Epstein, Jarstad and Stulting report no relevant financial ties.

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Cataract Surgery in Advanced Glaucoma

These patients require careful planning and taking extra care to ensure the best possible outcome.

Yvonne Ou, MD, San Francisco

Cataract surgery is the most frequently performed surgery in the world, but it can be complicated by many factors—including a coexisting disease such as glaucoma. In that situation, the cataract surgeon needs to make a number of adjustments to ensure a good outcome, especially if the patient has *advanced* glaucoma.

Here, I'd like to discuss eight things you can do to ensure the best possible outcome when performing cataract surgery in this circumstance.

1 Do careful surgical planning. This means answering several questions ahead of time:

— ***If the advanced glaucoma is uncontrolled, should you combine the glaucoma and cataract procedures or perform them separately?*** If the advanced glaucoma isn't well-controlled, you need to prioritize the glaucoma surgery. That means either doing the glaucoma surgery first and waiting to do the cataract surgery, or doing them both at the same time.

One advantage to combining the procedures is that doing so can simplify a filtering surgery. You might not need to do an iridectomy, and that might help to minimize postoperative inflammation. Also, placement of a tube in the sulcus can be much easier in a pseudophakic eye.

However, specific factors tied to the individual's situation could make staging the surgeries a better option. If the patient has pseudoexfoliation, for example, the eye might have a small pupil and weak zonules. You might need to insert a capsular tension ring during the cataract removal, and there might be a high risk of vitreous loss. In that situation it might be preferable to avoid doing both surgeries at the same time. Also, a combined procedure wouldn't be advisable if you hope to implant a toric lens, because a bleb or tube shunt can have an unpredictable effect on astigmatism.

However, if you decide to do the glaucoma surgery first and postpone the cataract surgery, two problems will arise. First, the glaucoma procedure is likely to accelerate cataract progression. Second, if you create a bleb, subsequent cataract extraction could lead to bleb failure. Studies have shown that the longer you wait between the trabeculectomy and the cataract surgery, the better the chances that the trabeculectomy bleb will survive the cataract surgery—but the longer you wait, the worse the cataract will become.

— ***If the glaucoma is well-controlled, should you add a MIGS procedure to the cataract surgery to reduce the patient's medication burden?*** We generally think of MIGS surgery as being reserved for mild to moderate glaucoma, but in a patient with well-controlled advanced glaucoma, a MIGS procedure can decrease the medication burden. If the patient is intolerant of some of the medications being taken, or simply wants to reduce the medication burden, it might make sense to consider MIGS surgery.

— ***Which type of intraocular lens is most likely to produce a good outcome?*** The vast majority of these patients receive aspheric monofocal IOLs. If the patient has astigmatism, there's some reason to consider implanting a toric IOL; they've been shown to improve vision in patients with advanced visual field loss.[1]

However, there are several challenges in this situation. The first challenge is getting stable readings

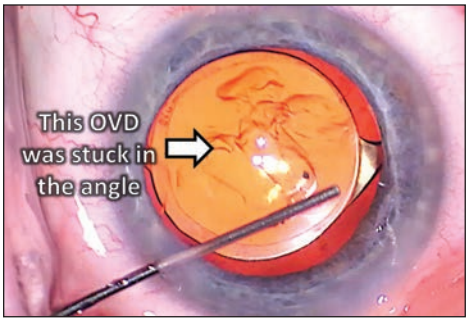
This article has no commercial sponsorship.

at the cornea in order to choose the appropriate IOL. (If the patient's prior trabeculectomy has been stable for some time, you probably can get good measurements.) But if you're thinking about doing a combined cataract and glaucoma surgery, there's an even more daunting challenge: It's very hard to predict what impact the trabeculectomy will have on the astigmatism. (MIGS surgeries are more astigmatically neutral, so a MIGS procedure might allow you to more accurately plan for a toric lens.)

Of course, multifocal IOLs are generally not advisable for anyone with advanced glaucoma; they undercut contrast sensitivity, which is already a problem for an advanced glaucoma patient.

— ***Is the patient truly going to benefit from cataract removal, or should you consider postponing the surgery?*** Even when an individual has significant damage from advanced glaucoma, it's been shown that removing a cataract improves both best corrected visual acuity and quality of life. For example, a study in the *Journal of Glaucoma* looked at 93 patients with both cataract and advanced glaucoma.[2] They measured pre- and postoperative vision-related quality of life, BCVA and weighted-average LogMAR vision. All subjects improved after cataract surgery, in terms of general vision, mobility, psychological adjustment, reading, fine work and activities of daily living.

Nevertheless, it's not always clear that removing the cataract in a patient with advanced glaucoma will improve the patient's vision. If the cataract is fairly advanced, it may be difficult to tell how much of the vision impairment is due to the cataract and how much is attributable to the glaucoma. This is an issue because cataract surgery is riskier in these patients, so you have to weigh the risks and benefits of doing the cataract surgery.



Viscoelastic often remains hidden in the nasal angle after standard visco removal techniques. Pushing a little BSS into the nasal angle at the end of the case, as described by Uday Devgan, MD, will reveal it, allowing its removal.

2 Manage expectations (your own and your patient's). Make sure that both you and the patient have an accurate sense of what you can realistically do for him in this circumstance. (This should be reflected in the informed consent.) Issues include:

— ***You can only correct vision loss from the cataract, not from the glaucoma.*** The patient shouldn't expect this procedure to restore the vision he or she had earlier in life.

— ***A postoperative IOP spike is possible.*** If your patients aren't warned about this, they may believe you did something wrong when their IOP rises and needs to be managed.

— ***If patients have had a prior trabeculectomy, they need to understand that cataract surgery could affect the bleb.*** The patient should understand that bleb failure is possible, and that separating the cataract and glaucoma procedure could lessen the risk.

— ***A prior trabeculectomy patient should consent to your performing a bleb revision and/or antimetabolite injection.*** In somes cases these could become necessary.

— ***Warn patients that the cataract removal may not result in a lower IOP.*** Given patients' access to information today, they may expect the cataract surgery to lower their IOP and conclude you didn't do the surgery properly if it fails to happen.

However, clinical data suggests that a pressure drop may not happen in patients with advanced open-angle glaucoma. First of all, patients who are well-controlled or have a low pressure don't generally have an IOP drop after cataract extraction.[3] And, in patients with a prior trabeculectomy, the IOP may even increase because the cataract surgery can cause inflammation and scarring in the bleb.[4] You should include this possibility in your discussion and informed consent.

3 Do what you can to prevent a postoperative IOP spike. Keep in mind all of the factors that can increase the likelihood of a postoperative IOP spike, and do what you can to mitigate them. Also, as noted earlier, include the possibility of a postoperative IOP spike in your discussion with the patient and in the informed consent.

Factors increasing the risk of a postoperative IOP spike include:

— ***The presence of glaucoma—especially pseudoexfoliation.*** Studies have found that patients with pre-existing glaucoma (especially pseudoexfoliation) tend to have a more complex cataract surgery, and are likely to have potentially harmful IOP spikes between three and seven hours after surgery.[5,6] Another study found that even medically well-controlled glaucoma patients often experienced IOP spikes.[7]

— ***The type of viscoelastic you use.*** Cohesive viscoelastic is less likely to cause an IOP spike than a dispersive viscoelastic, primarily because it's easier to completely remove at the end of surgery. For example, one study found that Viscoat caused significantly higher IOP increases and significantly more IOP spikes (and higher-pressure spikes) than DuoVisc

in the early postoperative period.[8] Another study found that this was also true when comparing Viscoat to Healon 5 following small-incision cataract surgery.[9]

— ***A long axial length; a previous trabeculectomy or laser trabeculoplasty; and a greater number of glaucoma medications.*** These were associated with an increased risk of postoperative IOP spikes in a study of this topic conducted at the University of Washington.[10] (The correlation to a greater number of preoperative glaucoma medications may be a surrogate for how advanced the patient's disease was.)

A common way to lower the risk of a postoperative IOP spike is to give the patient a pressure-lowering drug before or after surgery. Agents used for IOP spike prophylaxis include oral acetazolamide, Miostat and topical anti-hypertensives, including combination drops such as CoSopt (Merck).[7,11-13]

It turns out that timing counts; when the prophylactic agent is given to the patient can make a big difference in how effective it is. A study done in 2017 compared the impact of timing when giving oral acetazolamide to 90 open-angle-glaucoma patients with moderate to advanced glaucoma with 90 eyes undergoing cataract surgery.[14] The researchers randomized the groups to either one hour preoperatively, three hours postoperatively, or no medication at all. Then they measured the pressure at multiple time points to see how many eyes had a significant pressure spike, defined as more than 100 percent above the preoperative IOP.

They found that the patients receiving the drug one hour preoperatively did the best; they were least likely to reach that threshold. If the drug was given orally three hours after surgery, IOP elevation wasn't reduced until five hours or more after surgery.

This is very practical information. Before I saw this paper I was giving my patients oral prophylaxis after the surgery, which this study showed is inferior to one hour preoperatively. Furthermore, I'd been using an extended-release tablet; the good outcomes in the study were achieved with an immediate-release tablet. I always found a good pressure when seeing the patient the following day; that led me to believe I'd prevented a pressure spike. But this study makes it clear that giving oral acetazolamide one hour preoperatively—using immediate-release tablets—is a better way to prevent IOP spikes four to six hours after surgery.

Cortex left behind has been associated with increased inflammation.

Note: If you're combining cataract surgery with trabeculectomy, avoiding hypotony is also a concern. In that situation, you may want to plan for laser suture lysis after the first postoperative week. Hypotony will be less of an issue if the added surgery is a MIGS procedure, since the risk of hypotony is lower with MIGS.

4 Minimize inflammation. Two strategies can help ensure that postoperative inflammation is minimal. First, manipulating the iris will increase inflammation. So, to enlarge the small pupil, try using a bolus of intracameral lidocaine or a viscoelastic such as Healon 5. (Of course, if necessary, use whatever iris expansion technique you feel comfortable with.) Second, make sure you take the time to remove all of the cortex before completing the surgery. Cortex left behind has been associated with increased inflammation.

5 Remove all viscoelastic. Because you want to maintain the anterior chamber depth throughout the surgery—especially in hyperopic eyes and those with prior filtering surgery—you're going to use a lot of viscoelastic. If the patient has had a prior filtering surgery, some of that viscoelastic may try to exit the eye through the filter, making it more challenging to maintain adequate anterior chamber depth during surgery. To ensure the best possible outcome, you need to remove all of that viscoelastic. It's worth spending extra time to make sure you do—especially if the patient is a high myope. High myopes have larger eyes, so you've probably injected a substantial amount of viscoelastic, and it can be hidden.

To ensure you remove all of it, be sure to sweep behind the IOL. Then, carefully remove all the viscoelastic in the anterior chamber. Finally, do the "angle sweep" described by Uday Devgan, MD. The idea here is that when we inject viscoelastic into the eye at the beginning of the surgery, we tend to inject it into the nasal angle, because your cannula is coming in from the temporal incision. When performing the "angle sweep" the surgeon pushes a little BSS into the nasal angle at the end of the case. You'll be surprised how much unseen viscoelastic will appear as a result of this maneuver. *(See image, p. 55.)*

You can see an example of this technique, and its results, at cataractcoach.com/2018/11/19/the-angle-sweep-technique-to-remove-viscoelastic/. In the video, it looks like Dr. Devgan has done a great job of removing all of the viscoelastic in the standard manner. Then he takes the cannula and injects some BSS into the nasal angle—and a significant amount of retained viscoelastic appears. That's why the "angle sweep" is a technique

that's worth learning.

6 If the patient has had prior trabeculectomy, protect and/or revive the bleb. A number of maneuvers we make during cataract surgery could easily result in contact with an existing bleb. In order to avoid causing unintended problems, it pays to be conscious of this and go out of your way to avoid making contact.

Also, give some thought to where you place your paracentesis, especially when operating on a right eye. That's because in a right eye with a trabeculectomy, the bleb may be positioned right where you'd normally make the paracentesis.

Finally, consider injecting a little subconjunctival 5FU at the end of the case (as long as there's no contraindication). Performing surgery on the eye causes inflammatory metabolites to increase, and those will end up passing through the bleb. Injecting a little 5FU helps to prevent this from causing scarring. Studies have found that doing so has a protective effect on a functioning bleb and can be used routinely at the end of phacoemulsification in such cases.[15] I usually inject it inferiorly, away from the bleb; it diffuses and has the effect on the bleb that I want. Some surgeons might inject it adjacent to the bleb; I just feel more comfortable injecting it 180 degrees away.

It's possible that the bleb may need revision. To get a sense of how well the bleb is functioning—if you're not sure—you can inject trypan blue into the eye. A 2018 study used this approach, grading the blebs as having mild or diffuse staining; at one year postop, there was a trend toward needing more IOP-lowering medications among those eyes that had only mild bleb staining, although the difference wasn't statistically significant ($p<0.10$).[16]

If the bleb is working fine, I wouldn't touch it. I'd just try to do the shortest, cleanest cataract surgery I can and then inject a little 5FU as described above. If bleb function is suboptimal, you can consider doing *ab interno* revision, or *ab externo* needling along with the 5FU injection.

7 Schedule frequent follow-up. Given the higher risk of a postoperative IOP spike, you may want to see these patients more often than a routine cataract patient, especially in the day or two following the surgery. This is especially important if the patient has had a prior trabeculectomy or tube shunt, to monitor for IOP issues and early signs of bleb failure. (All surgeons have their own preferences for scheduling follow-up visits, so there's no specific formula that should be followed.)

One suggestion I haven't yet tried is scheduling an advanced-glaucoma patient early in the day. This gives you the option of asking the patient to stay in the office or ASC for several hours, so you can easily do a same-day IOP check and treat if necessary.

8 Increase the frequency of steroids compared to a typical phaco case, and consider the use of postop antimetabolites. For a routine patient, I'd prescribe prednisone 1% four times a day postop, but if the patient has a prior trabeculectomy or tube surgery, I might have the patient use it hourly or every two hours initially, to make sure the bleb stays functional. I'd have the patient do that for the first week, followed by a gradual taper. I'd also consider additional subconjunctival injections of 5FU in patients with prior trabeculectomy, especially if the bleb isn't functioning as it should be.

An Ounce of Prevention

Taking steps like these will help ensure that any cataract patient with advanced glaucoma avoids unwanted problems during surgery and isn't disappointed because of unrealistic expectations postoperatively. That will mean a better outcome, a happier patient and less worry for you. REVIEW

Dr. Ou is an associate professor of ophthalmology, co-director of the glaucoma division and vice chair for postgraduate education in the Department of Ophthalmology at the UCSF School of Medicine in San Francisco. She is a consultant for Merck.

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The Incoming Wave of AI in Retina

A look at both the potential benefits—and possible drawbacks—of artificial intelligence.

Grayson Armstrong, MD, MPH, Boston, and Ehsan Rahimy, MD, Palo Alto, Calif.

Ophthalmology has long been an early adopter of new and innovative technologies in patient care. The advent of optical coherence tomography in the early 2000s for evaluation of the retina quickly revolutionized daily clinical practice. In the past few years, the use of viral vectors to enable *in vivo* gene alterations to cure genetic disease became available in ophthalmology well before any other field with the U.S. Food and Drug Administration approval of Luxturna (voretigene neparvovec-rzyl, Spark Therapeutics) in 2017. Most recently, artificial intelligence technologies entered the field of ophthalmology. In April 2018, the FDA approved the first fully-autonomous AI-enabled screening device for diagnosing ophthalmic disease, the IDX-DR.

AI is a burgeoning field, and as the capabilities of machine learning and AI in ophthalmology continue to expand, new technologies will undoubtedly continue to emerge that will augment our practices and enable clinical insights never before thought possible. In this article, we'll take a look at the benefits and limitations of this technology.

What is Artificial Intelligence?

Artificial intelligence is a broad discipline under the umbrella of computer science that aims to enable computers to perform tasks usually done by humans.[1] AI algorithms allow computers to function intelligently and independently. Machine learning is a subset of AI that uses computer algorithms known as neural networks to allow computers to learn from datasets and subsequently edit their own coding with the goal of making future predictions about new data.[2] The ability of computers to learn mimics the capabilities of human intelligence, hence the use of the terms "artificial intelligence" and "machine learning."

Ophthalmology is uniquely capable of capitalizing on the promise of AI. Ophthalmologists generate robust amounts of data during routine clinical practice, such as visual acuity, intraocular pressure and the cup-to-disc ratio, along with ancillary imaging data from fundus cameras, OCT machines and visual fields. Machine learning algorithms require large amounts of data in order to learn. While machine learning and AI algorithms can be applied to a myriad of data sources (i.e., written text, audio, images, video), one of the most well-established use cases is screening for and diagnosing disease using clinical images (i.e., fundus photos) paired with clinical data.

To date, researchers have used machine learning algorithms to screen for and diagnose multiple ophthalmic diseases such as diabetic retinopathy, age-related macular degeneration, macular edema, glaucoma, keratoconus, post-LASIK corneal ectasia, retinopathy of prematurity, and cataracts.[1] It has also proven useful for predicting the prognosis of various ophthalmic diseases.

Commercially Available AI

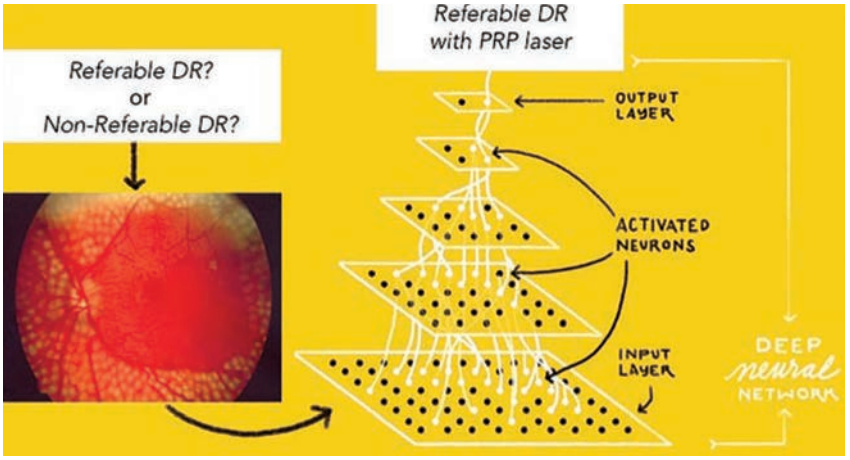
As mentioned earlier, the IDx-DR (IDx, LLC, Coralville, Iowa, USA) was the first autonomous AI system capable of screening for disease independent of a physician. IDx-DR uses a machine-learning-algorithm-equipped standalone fundus camera to screen for DR in diabetic patients; it's meant to be used by primary care physicians to identify patients requiring a referral to an ophthalmologist

for further management.[3-6] Years of research by the University of Iowa's Michael Abramoff, MD, PhD, and colleagues established the clinical efficacy of machine learning to use retinal photos to detect referable DR.[4] Studies of the technology's implementation in various primary care office settings supported the clinical trials, leading to eventual FDA approval. Of note, the IDx-DR algorithm only lets the primary care provider know if the patient has DR worrisome enough to be referred to an eye doctor, termed referable DR, which equates to moderate non-proliferative DR or worse. It doesn't report on the absence of diabetic retinopathy or the presence of mild DR not requiring referral.

Another technology on the horizon is a home-based OCT device from Notal Vision (Notal Vision Ltd, Tel Aviv, Israel), which uses a machine learning algorithm trained on patients with exudative retinal diseases such as DR and AMD.[7] Notal's home-based OCT machine is intended to be used by high-risk patients, and may autonomously detect changes in retinal morphology with accumulation of new fluid. If such worsened disease activity is detected, the patient's ophthalmologist is directly contacted. Notal received a "breakthrough device" designation from the FDA in 2018, and expects the device to be commercially available by 2020.

Research in Retinal Disease

AI in ophthalmology has focused most heavily on the field of retina. This makes sense, given the large number of images captured by retina specialists, the variety of imaging modalities capable of evaluating the retina, and the vast burden and vision-threatening nature of retinal disease. Multiple fundus photograph databases exist, and clinical use of OCT is prevalent, making the accumulation of these images easy for AI researchers.



A neural network for diabetic retinopathy screening. Patterns are presented to the network via the "input layer," which communicates to one or more "hidden layers" where the actual processing is done via a system of weighted connections. The hidden layers then link to an "output layer" where the result is given.

Diabetic retinopathy screening and diagnosis is a major focus within AI. Most AI-based diabetic retinopathy screening programs have focused on identifying diabetic patients with referable DR.[4-6,8-12] As a benchmark, a 2004 study found that ophthalmologists have a 73-percent sensitivity and 91-percent specificity in their ability to detect diabetic retinopathy on a dilated fundus examination.[13] By comparison, in 2016, Google published a novel study in *JAMA* showing that referable DR could be identified with a sensitivity of 97.5 percent and a specificity of 98.5 percent using fundus photos alone.[8] A separate larger study which validated its algorithm on a more varied multi-ethnic patient population reported sensitivities and specificities as high as 91 percent and 92 percent.[9]

It's worth noting that more robust algorithms more applicable to real-world populations can result from the use of datasets with more diverse metrics, such as more heterogeneous populations and varied fundus camera modalities. Additional studies have shown promise in stratifying between various stages of DR, such as mild, moderate or severe non-proliferative DR and proliferative DR.[8,9,14] Lastly, researchers recently reported the ability to reliably detect the presence of diabetic macular edema using color fundus photos alone.[15]

Screening and diagnosis for AMD have also been a focus of AI researchers. Using fundus photographs, OCT, or a combination of the two, researchers have been able to identify normal patients as well as those with evidence of AMD, to delineate areas of pathologic retinal fluid, and to grade the severity of AMD present.[7,16-18] Fundus autofluorescence imaging has also been used to automatically discern areas of geographic atrophy.[19]

Perhaps more interesting than disease detection is the ability of machine learning to prognosticate on various clinical outcomes in patients with retinal disease. With 96-percent accuracy, a neural network was able to use color fundus photographs to predict which diabetic patients would need laser or surgical intervention versus no intervention at all.[20] A second AI algorithm could use OCT retinal imaging to predict the need for an anti-VEGF injection in patients with neovascular AMD.[21] Yet another machine learning algorithm could predict which eyes with intermediate AMD were most likely to progress to advanced disease

(i.e., neovascular AMD or GA) based on OCT findings in combination with demographic and genetic factors with relatively high accuracy.[22]

While predicting disease progression can be useful to the clinician, predicting future visual acuity for patients with eye disease could be extremely beneficial for both the clinician and the patient. In one study, using the baseline OCT characteristics and demographic information of patients with diabetic macular edema, an AI algorithm could reliably predict visual acuity within 6.4 letters at one year and 6.81 letters at two years following an injection of ranibizumab.[23] In AMD, a separate AI algorithm using OCT images and clinical data could predict a patient's VA within 8.6 letters at one year.[24]

AI Beyond the Retina

Even though the majority of AI-related research has focused on the posterior pole, anterior segment pathology and glaucoma have seen advances as well.

• ***Anterior segment disease.*** Automated cataract grading systems using AI have been developed for both adults and children, the latter of which can even discern which pediatric cataracts are most likely to require surgical intervention to preserve vision.[25,26]

Corneal ectatic disease has also received the attention of AI researchers, given the relative difficulty of detecting diseases such as keratoconus early on and the relatively recent availability of corneal cross-linking in the United States to help slow or halt the progression of ectasia, as well as these conditions' potential for long-term visual morbidity. Using Scheimpflug data, corneal OCT imaging or a combination of the two, multiple algorithms have demonstrated reliable detection of keratoconus, with sensitivities and specificities of up to 100 percent.[27-30] Others have reliably identified patients who are at risk of developing corneal ectasia after LASIK surgery, an AI application which stands to benefit refractive surgeons immensely.[31]

Lastly, using retinal photographs alone, a Google-led team of machine learning researchers showed success in predicting a patient's spherical equivalent refractive error with a mean absolute error of 0.56 D.[32] This finding, along with many others listed above, highlight some of the ways in which computer-based AI harnesses the power and potential of machine learning to improve clinical decision-making, which can augment the clinical abilities of physicians.

• ***Glaucoma.*** Glaucoma has also received considerable attention.[33-36] Given the multiple data sources used by clinicians to test for glaucoma, machine learning is an ideal tool for assimilating the various testing modalities available to clinicians to screen for and diagnose glaucoma, such as visual fields, OCTs of the retinal nerve fiber layer and intraocular pressure readings. However, algorithms requiring much less data have also shown utility in accurately detecting glaucoma. Widefield OCT of the retina encompassing the optic nerve, as well as fundus photography, have each shown utility in detection of glaucoma and may simplify screening if users can make a diagnosis using the simplicity of single-image testing.[35,36]

Future Promise of AI

AI stands to support ophthalmologists' clinical decision-making by supporting screening efforts, diagnostics and the prediction of diseases and their prognoses. It isn't hard to imagine a future where the plethora of data collected from the medical record are combined with new data generated during a clinical visit, with the result being an AI report that helps with clinical decision-making. If computers are able to process the large volume of clinical data for each patient, the physician can spend more time considering the diagnosis and management plan and less time with data analysis. Improved information at the fingertips of ophthalmologists stands to improve patient outcomes and streamline clinical practice.

Machine learning may also be able to detect the presence or risk of developing both ophthalmic and systemic disease using eye imaging. Ophthalmic imaging is unique in that it allows doctors to directly assess blood vessels, neural tissue and connective tissue in living patients with high image quality and without the need for surgical pathologic specimens. Already, ocular images have proven useful in making medical assessments beyond eye-specific disease and have provided insights into patients' overall health. For example, researchers have reported the ability to predict a patient's age, gender, smoking status and systolic blood pressure based solely on retinal fundus photos.[37]

AI may also improve patients' access to eye care, since remote and teleophthalmic screening initiatives could be combined with AI-enabled technologies to help diagnose and treat eye disease, thereby preventing vision loss. AI technologies, once developed, require fewer resources to operate than laborious, time-intensive and expensive human-led screening programs. Additionally, AI-based systems can realize cost savings when compared to in-person clinical visits and manual image grading.[38]

Limitations

While there is considerable promise from AI, it's not without potential risk.

First, there is a risk of deskilling the workforce with implementation of AI technologies. For example, if clinicians are aided to the point of not needing to diagnose disease on their own, then they may become reliant on the technology and may lose or blunt their

diagnostic abilities.

Second, despite the impressive diagnostic accuracy of AI programs, some algorithms result in relatively high false-negative rates of detection of disease, which means that the algorithms incorrectly classify eyes as being disease-free or not requiring further evaluation. False negatives of this nature could be clinically disastrous for patients' vision, highlighting the need for continued improvement in AI technology and appropriate interpretation of AI algorithm results.

Additionally, gaining patient trust in the use of automated AI screening and diagnosis is likely to be a hurdle. Studies show that many patients are willing to embrace machine learning in medicine, but that there are still patients who don't trust computer-aided diagnosis and prefer in-person ophthalmic visits.[39] Lastly, it's not always obvious how a computer algorithm came to its clinical conclusion. Little insight into the "thought process" behind AI causes a "black-box" problem, whereby clinicians are left to trust the AI system blindly without being able to evaluate the value of the metrics used by the computer program.

In conclusion, artificial intelligence and machine learning in ophthalmology are enabling computer-assisted screening, diagnosis and prognostication of ophthalmic disease. Ophthalmology is uniquely poised to capitalize on the benefits of machine learning, given the abundance of clinical data and multimodal imaging generated in the field. Machine learning algorithms have been used in commercially available products, and have been applied in research applications focused on both anterior and posterior segment diseases. Advances in ophthalmology-specific AI stand to increase patient access to clinical screening and diagnosis as well as decrease health-care costs, especially when applied to high-risk populations, low-resource communities or when combined with telemedicine initiatives. REVIEW

Dr. Armstrong is chief resident in ophthalmology at Harvard University Medical School (AY 2019-2020) and director of the Ocular Trauma Service at the Massachusetts Eye and Ear Infirmary. Dr. Rahimy is a vitreoretinal specialist at the Palo Alto Medical Foundation.

Dr. Armstrong is a founding member of a tele-medicine ophthalmology device company, OculAR Technologies (OculAR, Boston). Dr. Rahimy is a consultant for Google.

You can contact Dr. Armstrong at: 243 Charles St., Boston, MA 02114. Phone: (617) 523-7900; fax: (617) 573-4028; email: grayson_armstrong@meei.harvard.edu.

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A teenager with a recurrent conjunctival lesion that prompts a referral to the Wills Eye Ocular Oncology Service.

Dilru C. Amarasekera, MD, Ralph Eagle, MD, Sara Lally, MD, and Carol Shields, MD

Presentation

A 14-year-old Caucasian boy presented for evaluation of a recurrent conjunctival lesion. The lesion had developed in the inferior fornix of his right eye eight months prior. He was first prescribed tobramycin/dexamethasone and prednisolone acetate drops for what was suspected to be a pyogenic granuloma. He had no improvement after one month and the medications were discontinued. By the end of the next month, his lesion resolved. Two months later the patient presented once again with recurrence of the same lesion. At this point, he was referred to a pediatric ophthalmologist for excisional biopsy, and histopathology disclosed a pyogenic granuloma. Two months later, the lesion recurred once again, prompting referral to Wills Eye Hospital Ocular Oncology Service.

Medical History

He had no reported past ocular history. He didn't wear glasses or contact lenses. He had no prior medical conditions. Family history was notable for lung cancer in his paternal and maternal grandmothers and thyroid cancer in his mother. The patient was a middle school student and played on the school's baseball team.

Examination

Ocular examination revealed visual acuity of 20/20 in both eyes. Pupils were round and equally reactive to light. Intraocular pressure was normal by finger tension. Confrontational visual fields and ocular motility were full. Anterior segment examination was notable for a firm, palpable, amelanotic 10 x 10-mm nodule within the tarsus of the right lower eyelid and a pedunculated, soft, vascular pyogenic granuloma in the adjacent inferior fornix *(Figure 1)*. Further anterior segment examination was unremarkable.

Dilated examination revealed normal vitreous, retina, choroid and optic discs bilaterally.

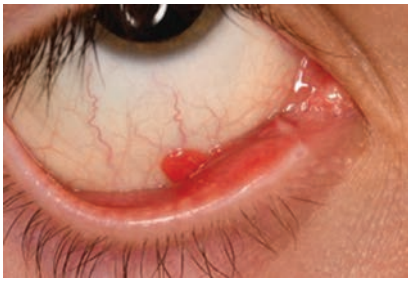

Figure 1. Conjunctival pyogenic granuloma in the inferior fornix of the right eye.

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p. 64

Workup, Diagnosis and Treatment

Upon presentation, nearly one year after the initial appearance of this conjunctival lesion, the patient was advised to have surgical excision and exploration for a suspected large, ruptured chalazion with associated pyogenic granuloma. In the operating room, the pyogenic granuloma was excised with wide margins, disclosing a 4-mm, open defect in the tarsoconjunctival tissue. Enlargement of the wound disclosed a wooden foreign body measuring 1.5 cm in length, extending into the orbit *(Figure 2 and 3)*. The wound was rinsed with antibiotics and partially closed to allow for drainage.

Histopathology demonstrated a mass composed of birefringent PAS-positive material consistent with wood. Foreign body giant cells and polymorphonuclear leukocytes were present. Several small, circular, black foci were noted grossly on the surface of the wood *(Figure 4)*. These proved to be colonies of pigmented fungal hyphae *(Figure 5)*. Examination of the conjunctival lesion revealed a mass of exuberant granulation tissue consistent with a pyogenic granuloma *(Figure 6)*.

Following identification of the wooden foreign body, the patient's mother recalled an incident one-and-a-half years prior when the patient had run into a bush chasing after a baseball and had suffered a small, cutaneous abrasion on the right lower eyelid with no residual trauma. Three months later, the first pyogenic granuloma appeared in close proximity to the area of prior trauma.

The patient was discharged on a regimen of oral amoxicillin for seven days and topical dexamethasone/neomycin/polymyxin B sulfate for three weeks. On follow-up evaluation one month later, the patient had complete healing of the wound with no recurrence of the conjunctival lesion or evidence of residual infection.

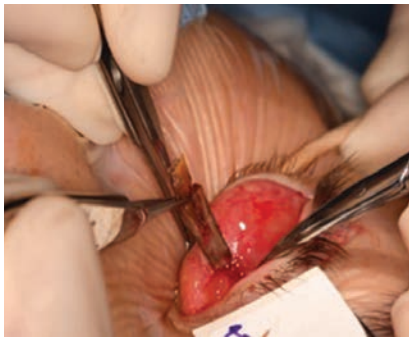

Figure 2. Intraoperatively, a large foreign body that appeared to be a piece of wood was removed from the inferior fornix.

Figure 4. The outer surface of the tree branch appeared to have a thin, white film over it with small, scattered foci of black dots, later found to be fungus.

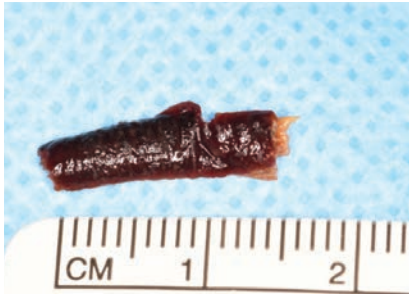

Figure 3. The wooden foreign body was 1.5 cm in length and represented a broken tree branch.

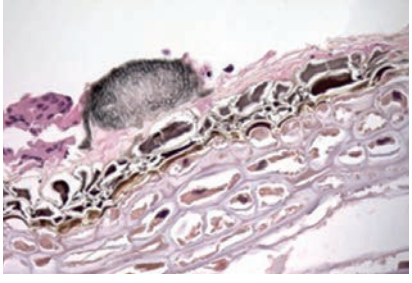

Figure 5. On histopathologic examination black fungus was noted on the surface of the wood.

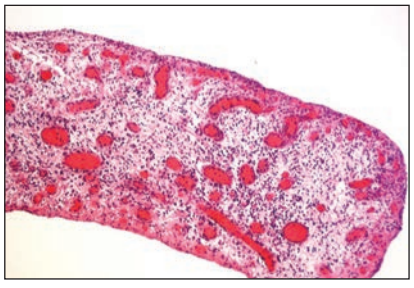

Figure 6. The pink mass proved to be exuberant granulation tissue, consistent with pyogenic granuloma.

Discussion

Intraorbital wooden foreign body (IOWFB) is a rare complication of penetrating ocular injury that can pose a particularly difficult clinical challenge for ophthalmologists. A component of this challenge stems from the rare nature of wooden foreign body injury to the eye. Management guidelines are based on several case reports[1-3] and small case series[4,5] described in the literature.

Often, as in this case, a prior history of trauma isn't volunteered at the time of clinical presentation. This may be because a wooden foreign body injury can occur remote from the time of clinical presentation. Additionally, this injury can occur in the pediatric population, who might not volunteer a history of trauma. Young males under 30 years of age are the prime targets

at risk for such injuries, and a high degree of suspicion should be kept when evaluating these patients.[4]

Presenting symptoms for IOWFB injury are variable. The literature describes a range of clinical complaints. One study described a series of nine patients with IOWFB, revealing common features of motility disturbance (five of the nine patients) as well conjunctival injection (again, five of the nine patients) with or without discharge. Less-common features included chronic drainage from an orbital fistula, decreased visual acuity and eyelid pain.[5]

The presence of a pyogenic granuloma in association with a deep-seated foreign body is rarely reported in the literature. In the orthopedic literature, there are a few cases detailing an association between recurrent pyogenic granuloma of the hand in association with an occult, retained foreign body.[6] In the ophthalmic literature, pyogenic granulomas have been reported in association with irritating or misplaced silicone punctal plugs.[7,8] Given the persistent, recurrent pyogenic granuloma presented in this case, the mass likely developed following a foreign body reaction to the wood.

The preferred imaging modality in patients with potential IOWFB injury is debated in the ophthalmic literature. A study by Wills Eye endorses computed tomography as the imaging modality of choice for identifying wood in the orbit. Bone windows are believed to be more effective than soft tissue windows at identifying IOWFB, as soft tissue windows—at their standard intensity of 200 to 350 Hounsfield units and level of 15 to 40 HU—are relatively inadequate to achieve wood resolution. Plain X-ray doesn't offer ancillary information, as it can't highlight wood. B-scan ultrasonography may or may not be helpful. The authors believed that magnetic resonance imaging could offer additional information to the CT scan as wood can appear hypointense relative to surrounding soft tissue and sometimes have ring-enhancing features on T-1 weighted imaging.[4] Other authors have argued that both CT and MRI should be considered when evaluating a patient with a potential wooden foreign body injury.[9-12]

By nature of the varied mechanisms of injury that lead to wooden penetration of the orbit, there's a high risk of intracranial penetration. Orbital bones can be fractured by high-velocity objects. Typically, wood acts as a low-velocity object that enters the orbit through the eyelid and is deflected by the globe, being directed towards the orbital apex. This location allows a port of entry for intracranial extension.[1] The risk of intracranial penetration should be kept in mind, and patients should undergo appropriate brain imaging to rule out this potentially fatal complication.

Wood, unlike other inert foreign bodies that are well-tolerated by the body, can result in a significant inflammatory or infectious reaction.[2,11] For this reason, management nearly always involves surgical removal, wide exploration and rinsing the site with antibiotics. Penetrating orbital injuries have been reported to have an infection rate of up to 64 percent; therefore, antibiotic coverage is recommended, in conjunction with surgical removal.[3] Some authorities recommend that clinicians use antibiotics with adequate blood-brain penetration, given the risk of intracranial penetration with a case involving an intraorbital wooden foreign body.[1]

Interestingly, empiric antifungal therapy is typically not recommended for IOWFB injuries, despite the presence of organic matter. This is due to the rarity of associated fungal infection and the relative toxicity of treatment regimens.[4] The patient discussed in this case was noted to have several foci of fungi on the wood that was extracted from his inferior fornix. Surprisingly, despite the presence of an undetected piece of wood in the orbit for more than a year, the patient didn't develop an infection. Given the patient's well-healed incision and lack of infection at the postoperative follow-up visit, a course of antifungal therapy was deemed unnecessary.

In summary, intraorbitals wooden foreign body injury is a rare and difficult-to-detect trauma that requires a clinician to maintain a high degree of suspicion. A recurrent pyogenic granuloma may be a clue to a deep-seated foreign body, especially in the appropriate population. A combination of imaging, including a CT scan and/or MRI, should be used to exclude intracranial involvement, a potentially serious complication of these injuries. Management of IOWFB injury typically involves surgical extraction of the wood, exploration of the tissue, antibiotic rinsing of the site and postoperative local and systemic antibiotic coverage. REVIEW

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BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

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

DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies 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 studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 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% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience
The following adverse reactions have been identified during postapproval 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 cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS
Pregnancy
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.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation 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.

Lactation
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. 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.

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.
Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.
Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

Shire

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.
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References:

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Indication

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

Important Safety Information

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

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, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

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