REVIEW® of Ophthalmology
June 2020
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ALTERNATE ROUTES IN GLAUCOMA

Surgeons discuss new technology and novel thinking about surgeries:

ALSO INSIDE:

Quench Dry Eye: **New SYSTANE® HYDRATION PF with HydroBoost Technology**

Laura M. Periman, MD

Ocular Surface Disease Specialist

Director of Dry Eye Services and Clinical Research

Seattle, Washington

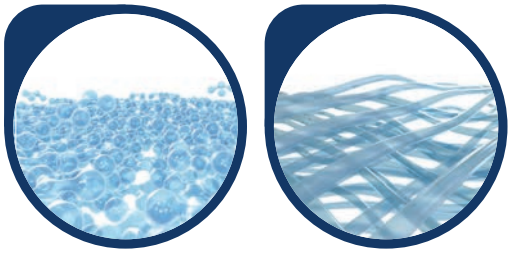
Ocular surgeons know the importance of checking for signs and symptoms of dry eye before surgery, and addressing it as needed. I trust the SYSTANE® family of artificial tears to provide real dry eye relief for my patients. The SYSTANE® family includes artificial tear solutions for a wide variety of patient types with varying levels of severity. Alcon's latest addition to the family, SYSTANE® HYDRATION PF (preservative-free), features HydroBoost Technology, a unique combination of ingredients that helps retain the active lubricants for longer-lasting hydration vs. SYSTANE ULTRA.[1,2*]

HydroBoost Technology

A unique combination of inactive ingredients which helps retain the dual active lubricants for lasting dry eye symptom relief without preservatives.[6]

Retention:
HP-GUAR

Hydration:
SODIUM HYALURONATE



The new SYSTANE® HYDRATION PF with HydroBoost Technology has special features that make it an excellent choice for the corneas of dry eye patients who need a preservative-free option. The unique formulation begins with the dual-action lubricants propylene glycol and polyethylene glycol 400,† which work to reduce dry eye symptoms.[3,4]

HydroBoost Technology is also added, consisting of the gelling agent HP-GUAR (present in all SYSTANE® products)[1,3] and sodium hyaluronate, the salt form of hyaluronic acid, a naturally-ocurring substance found in tears that has viscoelastic properties to help retain the active ingredients on the ocular surface and helps the lubricants provide long-lasting hydration.[1,2,4,5] Plus, as its name indicates, SYSTANE® HYDRATION PF does not contain any preservatives.

This formulation makes SYSTANE® HYDRATION PF with HydroBoost Technology an ideal choice for patients who need long-lasting, preservative-free relief from symptoms of aqueous-deficient dry eye.[6‡] This includes those experiencing frequent symptoms, requiring an artificial tear more than four to six times per day. It may also include patients with other types of dry eye requiring long-lasting symptom relief.

SYSTANE® HYDRATION PF artificial tears are available over the counter in boxes of 30 single-use, sterile vials. I always check for signs and symptoms of dry eye before ocular surgery, and will consider recommending SYSTANE® HYDRATION PF Preservative-Free Dry Eye Relief to quench the symptoms of dry eye with hydrating relief for my patients.

* vs. SYSTANE® ULTRA Lubricant Eye Drops; based on in vitro outcomes using SYSTANE® HYDRATION preserved formulation.
† These ingredients are also used in SYSTANE® ULTRA and SYSTANE® ULTRA PF.
‡ Based on outcomes on Ocular Surface Disease Index (OSDI) in subjects using SYSTANE® HYDRATION preserved formulation.

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1. Rangarajan R, Kraybill B, Ogundele A, Ketelson HA. Effects of hyaluronic acid / hydroxypropyl guar artificial tear solution on protection, recovery, and lubricity in models of corneal epithelium. *J Ocul Pharmacol Ther.* 2015;31:491-497. **2.** Alcon data on file, 2014. **3.** Davitt WF, Bloomenstein M, Christensen M, Martin AE. Efficacy in patients with dry eye after treatment with a new lubricant eye drop formulation. *J Ocul Pharmacol Ther.* 2010;26:347-353. **4.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf.* 2017;15:575-628. **5.** Rah MJ. A review of hyaluronan and its ophthalmic applications. *Optometry.* 2011;82:38-43. **6.** Mrukwa-Kominek E, Baranska K, Jadczyk K. First clinical reports on the application of the modern dual-polymer formula in aqueous deficiency dry eye syndrome - Polish observations. Presented at the 20th European Society of Cataract & Refractive Surgery Winter Meeting; February 26–28, 2016; Athens, Greece.

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REVIEW NEWS
Volume XXVII • No. 6 • June 2020

How Susceptible is the Conjunctiva to COVID-19?

Researchers at the University of Hong Kong have found that SARS-CoV-2, the cause of COVID-19, replicates in the conjunctiva to a greater extent than the severe acute respiratory syndrome coronavirus that triggered the notorious SARS epidemic (SARS-CoV) that afflicted 26 countries with more than 8,000 cases in 2003.[1] In fact, one of the researchers, in an interview with the *South China Morning Post*, says SARS-CoV-2 is much more efficient in infecting the human conjunctiva and the upper respiratory airways than SARS, with virus level about 80 to 100 times higher, which might explain its high transmissability. However, the researchers and a leading corneal specialist in the United States, emphasize that the findings don't necessarily translate to an increased risk of transmission of COVID-19 through the conjunctiva.

In a study published in *Lancet Respiratory Medicine* on May 7, the researchers isolated SARS-CoV-2 from a patient with confirmed COVID-19 and compared virus tropism and replication competence with SARS-CoV, Middle East respiratory syndrome-associated coronavirus (MERS-CoV), and 2009 pandemic influenza H1N1 (H1N1pdm, Swine Flu) in *ex vivo* cultures of human

bronchus (n=5) and lung (n=4). The researchers also assessed extrapulmonary infection using *ex vivo* cultures of human conjunctiva (n=3) and *in vitro* cultures of human colorectal adenocarcinoma cell lines.

"This study shows what has been suspected—that conjunctival tissue can be infected with the SARS-CoV-2 virus," says Yuri McKee, MD, MS, a corneal and refractive surgeon at East Valley Ophthalmology in Mesa, Arizona. "In general, I don't think this is a significant source of transmission, especially as compared to airborne droplets from the respiratory system. Most personal protective equipment worn includes a mask and eye protection. This study didn't show that that transmission via the eye was by the airborne route. Instead, it shows that the conjunctiva can be a source of infection. The most likely vector for conjunctival infection is probably fingers near the eyes."

Kendrick C. Shih, MD, an ophthalmologist and one of the authors of the study, says his team's *ex vivo* research model was based on the group's previously published work comparing the differential ability of the 2009 H1N1 virus and the seasonal H1N1 virus to infect the conjunctiva.[2] "We believe this finding represents a first step into better understanding how SARS-CoV-2 invades and replicates itself in the conjunctiva," he adds. He recommended using "extreme caution" in translating the results into clinical practice, noting that other factors weren't modeled in the *ex vivo* system, including the effect of the eyelids, blinking and the tear film. "We also don't have evidence from our *ex-vivo* model that the virus spreads to the rest of the body through the blood stream," he continues. "Finally, the study doesn't examine whether the virus can then be spread from the conjunctiva of COVID-19 patients to others through tears, or through eye rubbing."

Dr. Shih adds that the study further supports the idea that conjunctiva may be a potential tissue through which SARS-CoV-2 enters the body and that its replication is 40-fold higher than that of SARS-CoV. "But there is little evidence from our work and other studies to support the conjunctiva as a route

Correction

In the May 2020 issue of *Review*, in the feature "Finding a New Normal," Peter Netland, MD's location was erroneously listed as "Charlotte" rather than "Charlottesville, Virginia." *Review* regrets the error.

FIRST AND ONLY
FDA-APPROVED TREATMENT FOR THYROID EYE DISEASE

IT'S TIME FOR A BREAKTHROUGH
IT'S TIME FOR TEPEZZA

TEPEZZA is proven to[1-4]:

- **Decrease proptosis[1]**
- **Improve diplopia[1]**
- **Reduce orbital pain, redness, and swelling[2,3]**
- **Improve functional vision and patient appearance[2,3]**

...in patients with Thyroid Eye Disease (TED), without concomitant steroids (vs placebo at Week 24).[2-4]

Learn more at TEDbreakthrough.com

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

References: 1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. **2.** Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352. **3.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. **4.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18)(suppl):1748-1761. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1614949/suppl_file/nejmoa1614949_appendix.pdf.

TEPEZZA™
teprotumumab-trbw

Significantly greater proptosis responder rate* (Study 2)[1,2]

TEPEZZA **83%** **TEPEZZA (n=41)**

vs

Placebo **10%** **Placebo (n=42)**

P<0.001 at Week 24

*Both the safety and efficacy of TEPEZZA were evaluated in 2 randomized, double-masked, placebo-controlled clinical trials (Studies 1 and 2) consisting of 171 patients with TED (84 were randomized to TEPEZZA and 87 to placebo). The primary endpoint in Studies 1 and 2 was proptosis responder rate, defined as having a ≥2-mm reduction from baseline in proptosis in the study eye at Week 24 without deterioration (≥2-mm increase in proptosis) in the non-study eye.[1]

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Please see Brief Summary of Prescribing Information for TEPEZZA on following page.

HORIZON

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions [see Warnings and Precautions]
- Exacerbation of Inflammatory Bowel Disease [see Warnings and Precautions]
- Hyperglycemia [see Warnings and Precautions]

Clinical Trials Experience

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

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase
c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor-1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There is insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss [see Data]. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA.

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breastfed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-Related Reactions

Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Inflammatory Bowel Disease

Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

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HORIZON

of spread of the virus to others," he notes. In fact, he adds, a recent clinical study conducted in Singapore demonstrated a significantly low SARS-CoV-2 RNA yield from the tears and conjunctival swabs of COVID-19 patients.[3] "To answer this question, we will require further clinical and laboratory-based studies for better evidence of transmission through the conjunctiva," says Dr. Shih.

Dr. Shih and his research colleagues note that ophthalmic care in Hong Kong is a "particularly high-risk area for spread of the virus" because of close face-to-face contact during exams, general overcrowding of public waiting areas and a potential risk of viral inoculation through the conjunctiva. "Ophthalmic centers have been amongst the first in stepping up precautions in the early days of the pandemic," he continues, adding that plastic barrier shields have been installed to provide protection at slit lamps. "Our group recently shared with ophthalmologists across the world our experience in maintaining our routine ophthalmic clinic service, as well as our elective cataract surgery service."[4,5]

Activities that are risks for generating micro-aerosols—including non-contact air-puff tonometry and those that involve tear, fluid or blood spillage, such as nasolacrimal duct syringing and incision and curettage of chalazia—were temporarily halted by clinicians in Hong Kong. Nursing staff assigned to apply eye drops for pupil dilation or topical anesthesia were at risk for splashes and were required to wear eye shields while performing these tasks, he adds. "With these measures in place, our clinics did not record a single case of COVID-19 infection amongst our staff and patients from the beginning of our introduction of precautionary measures on January 29 until April 19 of this year."

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5. Shih, KC, Wong JKW, Lai JSMet., Chan JCH. The case for continuing elective cataract surgery during the COVID-19 pandemic. J Cataract Refract Surg 2020; May 1. [Epub ahead of print].

AI Drusen Detection for Prediction of AMD Progression

Ophthalmologists at the Medical University of Vienna note that morphologic changes and their pathognomonic distribution in the progression of age-related macular degeneration aren't well understood. In an attempt to get a better grasp on these changes, they undertook a study to characterize the pathognomonic distribution and time course of morphologic patterns in AMD, and to quantify changes associated with progression in macular neovascularization and macular atrophy.[1]

The cohort study included optical coherence tomography volumes from study participants with early or intermediate AMD in the fellow eye in the HARBOR (A Study of Ranibizumab Administered Monthly or on an As-needed Basis in Patients With Subfoveal Neovascular Age-Related

(Continued on page 12)

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*In Home Use Test, March 2018. n=301. †LUMIFY is an OTC selective α2-AR agonist. [1]McLaurin E, Cavet ME, Gomes PJ, Ciolino JB. Brimonidine ophthalmic solution 0.025% for reduction of ocular redness: a randomized clinical trial. *Optom Vis Sci*. 2018;95(3):264-271.

BAUSCH+LOMB

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Ophthalmic Product Development Insights

Matthew Chapin *Andover, Mass.*

Managing Your Start-up During COVID-19

We have been in a "new normal" during the COVID-19 pandemic. In this installment of Ocular Product Development Insights, we'll briefly review some perspectives on how COVID-19 is impacting start-ups and new entrepreneurs with their business plans and fundraising, and the adjustments they're making in order to manage the situation.

There are many comparisons being drawn between the pandemic and the 2008 global financial crisis, since both have had severe financial impacts. Though the two differ in the speed and shape of the market reaction and recovery, their impact on macroeconomics and the official policy response, they both have in common high levels of uncertainty. Supported by regulations put into place after 2008, financial institutions were stronger in general going into the current crisis. We've seen a partial recovery of the market, and market volatility, though still high, has also decreased compared to the levels in March and early April.

When considering product development, uncertainty is the one constant. That said, the biotech index is at an all-time high (likely for multiple reasons), so the market is relatively healthy and still seeing investment despite the pandemic. Though there are delays in development processes in some cases, we've seen companies continue to be funded by institutional investors, other venture funds and strategic investors, and license deals still are being inked (e.g., the jCyte license with Santen announced in early May).

According to Strata Decision Technology, a company that makes software for tracking performance and analytics in health care, there has been up to an 81-percent decline in volume in ophthalmology compared to 2019. This is the highest decrease in volume among medical specialties, Strata says. For drugs, the updated sales and earnings reports, along with product revenues for the second quarter of 2020, will be key. While the overall growth rate of prescriptions slowed in the first quarter, in some cases sales were still up compared to prior quarters and Q1 2019. In other cases, sales plateaued or declined. Ophthalmic products are among the segments with the greatest decline in drug sales volume in recent months, driven by the fact that a large number of scripts for eye drops are typically used in non-emergent and elective cases, which had been halted for weeks. So, we'll have to see the updated reports down the road, if and how the decline in prescriptions impacts the funds allocated for investments in new products, and how the structure of deals are impacted, with the likely result being limited near-term cash payments.

Potential investors, existing investors and potential license partners will want to know how you plan to manage during the COVID-19 pandemic and how it will affect your development activities. Showing that you're prepared should be part of your plan. Ron Weiss, founding partner and principal of Infocus Capital Partners, a venture fund specializing in ophthalmology, offers the following advice to investors raising capital: "Try to be as transparent as possible," he says. "In addition to advocating for the attributes of the company, discuss where you see challenges specific to COVID-19, and be willing to discuss the competitive landscape in the context of the current situation."

Following are a few comments regarding key areas of development:

• ***Preclinical vendors.*** Speaking from the experience of our own preclinical group, lab activities—specifically, animal research—have recovered to near their normal operating levels, including the supply of the animals. However, currently there are delays in the supply of drugs and active pharmaceutical ingredients (API) coming in. So, with preclinical studies, it's more about building in additional pre-study time to account for delays in making and receiving supplies and drugs. GLP toxicology vendors and manufacturing facilities are making progress, though it's wise to build in additional lead times and stay in close contact with these entities regarding scheduling, as these are gating items for the clinical trials.

• ***Regulatory.*** We've seen that the Food and Drug Administration, European Medicines Agency and Japan's Pharmaceuticals and Medical Devices Agency have all been responsive, scheduling meetings without significant delay and responding to questions. Regulatory meetings have been converted to teleconferences, of course, but for the new entrepreneur it's helpful to know that more regulatory meetings have been conducted as teleconferences in recent years anyway. You can expect to receive the same quality feedback from the FDA on a conference call, and you shouldn't expect this to impact the regulatory guidance you'll receive.

• ***Clinical trials.*** The pandemic certainly has had an impact on the planning of clinical trials, the extent of which depends on the nature of the trial, the drug's indication and the centers involved. In general, studies involving indications that are sight-threatening, which require patients to come to the office for therapy (such as an intravitreal injection), are less impacted than those trials that are non-sight threatening, such as safety studies using normal, healthy volunteers. The patient enrollment for device studies that involve elective surgical interventions will most likely be impacted by the pandemic, especially if the study is being conducted in an academic institution.

The viability of trials that are planned for next year is difficult to predict. We anticipate that the situation will be more under control and sites will be back operating by then. But here are some things to keep in mind as far as more immediate timelines: If you have a trial planned this year, you need to consider performing a specific COVID impact assessment at the sites, which includes: collecting information on COVID cases; noting trends in the local geographic area; observing local recommendations at each site; learning how sites are handling non-essential patient visits; seeing how COVID has impacted regular operational processes at the sites; and digging into the pandemic's impact on patient recruitment at each site, with the understanding that private practice enrollment will differ from that in academic settings.

Companies need to be honest in their assessment of projected enrollment rates and consider whether they're treating an emergent issue or performing an elective procedure. One should consider building back-up sites into the study plan, to account for lower recruitment or situations in which some sites may be slower

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to begin than others.

All of this should be built into your COVID-specific risk-management plan that you communicate to potential or existing investors, to build confidence that you've thought things through. The time can also be used to pre-screen subjects for the study.

Clinical protocols should consider the guidelines issued by the FDA related to COVID-19's impact. These relate to how protocol deviations are handled, especially with scheduling, visit windows and how safety follow-up is done, including remote patient check-ins and virtual visits.

Telemedicine has been booming, and is now driven by the need for social distancing and benefiting the increased flexibility in some regulations (i.e., emergency telemedicine device approvals). Our clinical team at Ora is leveraging its virtual clinical trial offering (Virtual EyeSite) in response to COVID-19. Its objectives are to maximize the potential for at-home assessments using telemedicine, provide technological and logistics support of investigational product management and develop other innovations to support endpoint collection.

One example is the recent inclusion of a smartphone device for at-home imaging of the lid margin in a multicenter trial for atopic keratoconjunctivitis, (clinical trial code: NCT04296864).

• ***Planning/operations.*** With each of the above, the consistent message is that there is a higher level of uncertainty that your plans need to take into account. Create a strategy that'll let you hit the ground running when the pandemic ends. Doing this requires remaining in close and regular communication with vendors/collaborators so you're not relying on proposals with timelines that were defined prior to the pandemic. Overall, companies need to be in a cash conservation mode during fundraising (and post-funding). This may require deciding which activities are more important in order to advance the program. Focus on critical-path items needed to maintain timelines and drive decision making. Perform multiple analyses for different COVID-19 scenarios to show investors (potential or existing) that you have a handle on the situation and will be able to adapt to this changing environment in the future.

Review and comments on this column were provided by Aron Shapiro of the Corporate Development group at Ora Inc., and the clinical team members at Ora.

Mr. Chapin is senior vice president of corporate development at Ora, which offers device and drug consulting, clinical research and development, and strategy and support to catalyze new client and partner initiatives. The author welcomes your comments or questions regarding product development. Please send correspondence to mchapin@oraclinical.com or visit www.oraclinical.com

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(Continued from page 7)

Macular Degeneration) trial. Individuals underwent imaging monthly for two years (July 1, 2009, to Aug. 31, 2012) following a standardized protocol. Data analysis was performed between June 1, 2018, and Jan. 21, 2020.

To obtain topographic correspondence between individuals and over time, investigators mapped scans into a joint reference frame. They established time of progression to MNV and MA, and automatically segmented drusen volumes and hyperreflective foci (HRF) volumes in three dimensions using validated artificial intelligence algorithms. They constructed topographically-resolved population means of the markers by averaging quantified drusen and HRF maps in the patient subgroups. Here are some of the findings:

• Of 1,097 individuals enrolled in HARBOR, 518 had early or intermediate AMD in the fellow eye at baseline (mean age: 78.1 ±8.2 years; 59.7 percent female).

• During the 24-month follow-up period, 135 eyes (26 percent) developed MNV, 50 eyes (10 percent) developed MA and 333 eyes (64 percent) didn't progress to advanced AMD.

• Drusen and HRF had distinct topographic patterns. Mean drusen thickness at the fovea was:

— 29.6 µm (CI, 20.2 to 39 µm) for eyes progressing to MNV;

— 17.2 µm (CI, 9.8 to 24.6 µm) for eyes progressing to MA; and

— 17.1 µm (CI, 12.5 to 21.7 µm) for eyes without disease progression.

• At 0.5-mm eccentricity, mean drusen thickness was:

— 25.8 µm (CI, 19.1 to 32.5 µm) for eyes progressing to MNV;

— 21.7 µm (CI, 14.6 to 28.8 µm) for eyes progressing to MA; and

— 14.4 µm (CI, 11.2 to 17.6 µm) for eyes without disease progression.

• The mean HRF thickness at the foveal center was 0.072 µm (CI, 0 to 0.152 µm) for eyes progressing to MNV, 0.059 µm (CI, 0 to 0.126 µm) for eyes progressing to MA and 0.044 µm (CI, 0.007 to 0.081) for eyes without disease progression.

• At 0.5-mm eccentricity, the largest mean HRF thickness was seen in eyes progressing to MA (0.227 µm; CI, 0.104 to 0.349 µm), followed by eyes progressing to MNV (0.161 µm; CI, 0.101 to 0.221 µm) and eyes without disease progression (0.085 µm; CI, 0.058 to 0.112 µm).

Investigators found that drusen and HRF represented imaging biomarkers of disease progression in AMD, demonstrating distinct topographic patterns over time that differed between eyes progressing to MNV, eyes progressing to MA and eyes without disease progression. They added that automated localization and precise quantification of these factors may help to develop reliable methods of predicting future disease progression. REVIEW

1. Waldstein SM, Vogl WD, Bogunovic H, et al. Characterization of drusen and hyperreflective foci as biomarkers for disease progression in age-related macular degeneration using artificial intelligence in optical coherence tomography. JAMA Ophthalmol 2020; May 7. [Epub ahead of print].

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The first and only once-daily fixed-dose combination of prostaglandin + ROCK inhibitor

IOP — Nearly 60% of Rocklatan® patients achieved a target pressure of 16 mmHg or less[2]

The majority of ocular adverse events were mild and tolerable, with minimal systemic adverse events[1,3]

QD — Once-daily dosing relieves treatment burden and may improve adherence and treatment outcomes[1,4]

IOP: intraocular pressure; ROCK: rho kinase

Visit Rocklatan.com to learn more about this innovative drop for elevated IOP

IMPORTANT SAFETY INFORMATION

Contraindications
None.

Warnings and Precautions
- Pigmentation changes
- Eyelash changes
- Intraocular inflammation
- Macular edema
- Herpetic keratitis
- Bacterial keratitis
- Contact lens wear

Adverse reactions
Rocklatan®: The most common ocular adverse reaction is conjunctival hyperemia (59%). Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Netarsudil 0.02%: Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%: Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reaction.

Please see brief summary on the adjacent page.

For full Prescribing Information, please visit Rocklatan.com.

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.

INDICATIONS AND USAGE
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is approved for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose in the evening. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

References:
1. Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% Prescribing Information, Aerie Pharmaceuticals, Inc., Irvine, Calif. 2019. **2.** Asrani S, McKee H, Scott B, et al. Pooled phase 3 efficacy analysis of a once-daily fixed-dose combination of netarsudil 0.02% and latanoprost 0.005% in ocular hypertension and open-angle glaucoma. Presented at the 13th Biennial Meeting of the European Glaucoma Society, March 2018. **3.** Data on file. Aerie Pharmaceuticals, LLC. **4.** Prum B Jr, Rosenberg L, Gedde S, et al. Primary Open-Angle Glaucoma Preferred Practice Pattern guidelines. *Ophthalmology.* 2016;123(1):P41-P111.

aerie Pharmaceuticals, Inc.

Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%
Rx Only

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

INDICATIONS AND USAGE
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

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If one dose is missed, treatment should continue with the next dose in the evening. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Pigmentation
Rocklatan® contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Beyond 5 years the effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with Rocklatan® can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
Rocklatan® contains latanoprost which may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
Rocklatan® contains latanoprost which should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because it may exacerbate inflammation...

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

Herpetic Keratitis
Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost. Rocklatan® should be used with caution in patients with a history of herpetic keratitis. Rocklatan® should be avoided in cases of active herpes simplex keratitis because it may exacerbate inflammation.

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

Use with Contact Lenses
Contact lenses should be removed prior to the administration of Rocklatan® and may be reinserted 15 minutes after administration.

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

Rocklatan®
The most common ocular adverse reaction observed in controlled clinical studies with Rocklatan® was conjunctival hyperemia which was reported in 59% of patients. Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions reported were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Other adverse reactions that have been reported with the individual components and not listed above include:

Netarsudil 0.02%
Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%
Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reactions.

DRUG INTERACTIONS
Although specific drug interaction studies have not been conducted with Rocklatan®, in vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost ophthalmic solution 0.005%. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on netarsudil ophthalmic solution use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the RHOD, based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

For latanoprost, in 4 of 16 pregnant rabbits, no viable fetuses were present at a dose that was approximately 80 times higher than the RHOD. Latanoprost did not produce embryofetal lethality in rabbits at a dose approximately 15 times higher than the RHOD.

Lactation
There are no data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. It is also not known whether latanoprost or its metabolites are excreted in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rocklatan® and any potential adverse effects on the breastfed child from netarsudil and latanoprost.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

For additional information, refer to the full prescribing information at www.Rocklatan.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

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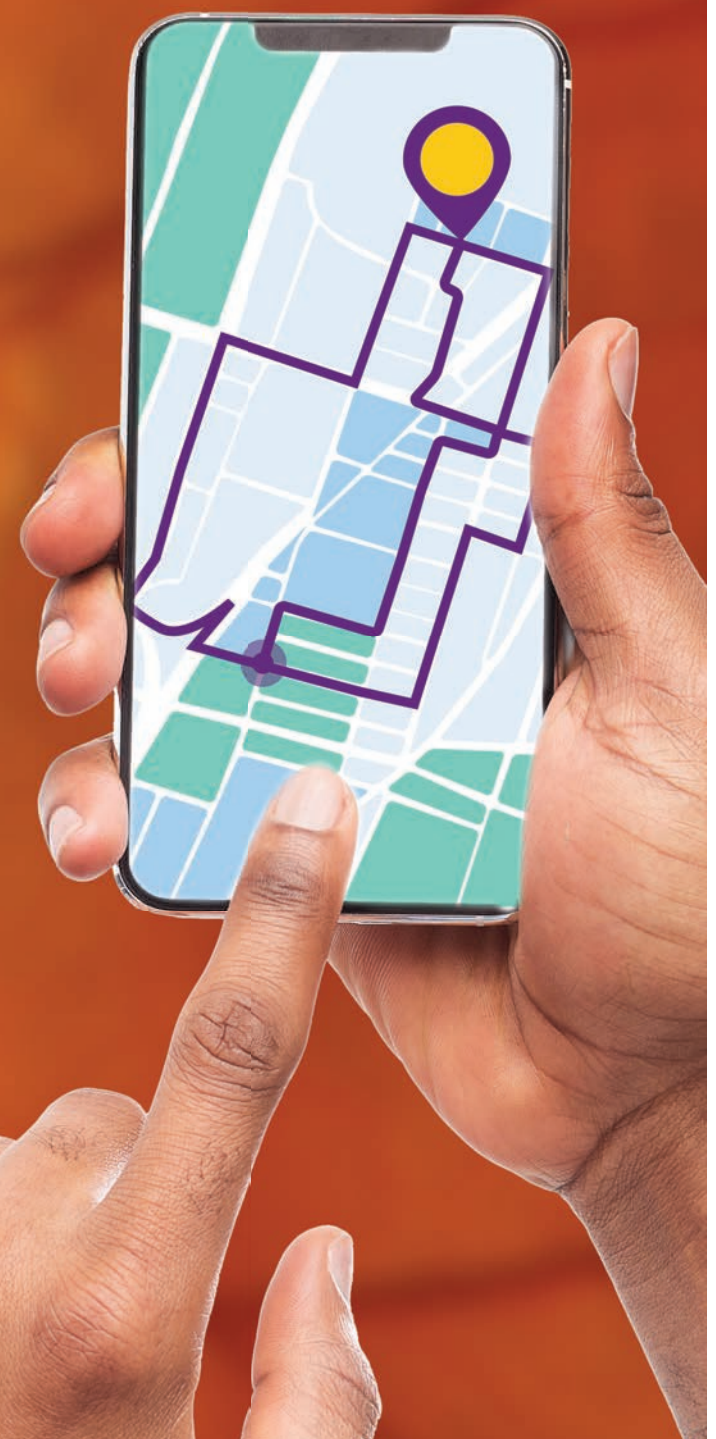

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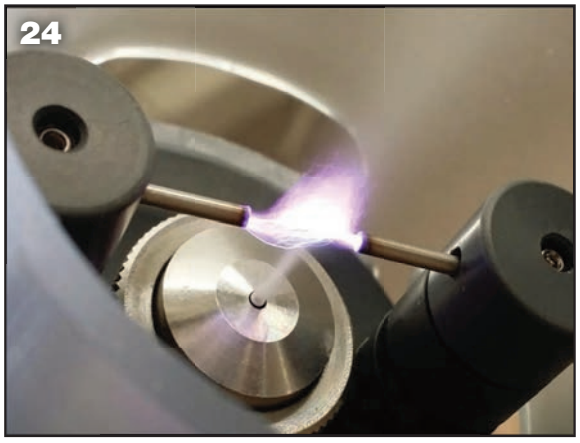

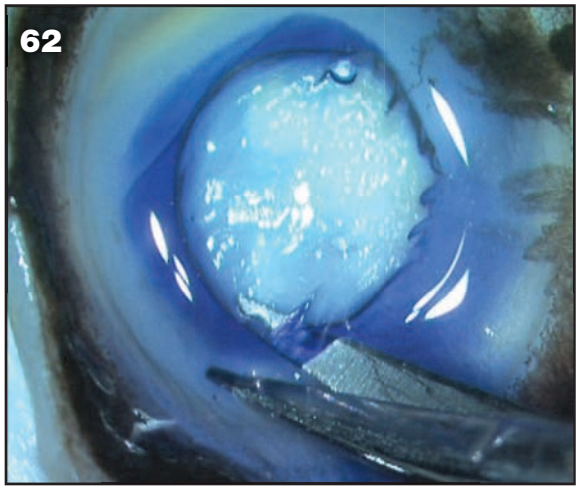

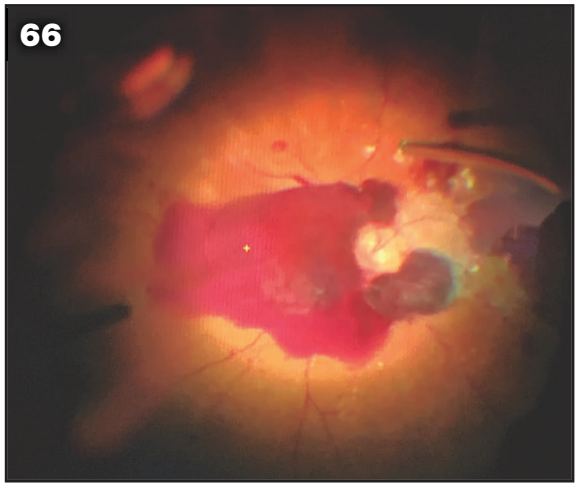

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JA011 Rev. 04/2020

Reopening Slowly And Safely

Cataract surgeons explain how they've minimized risks to patients and practice—and how they will turn things around.

Sean McKinney, Senior Editor

The final week of last month may have ended ophthalmic surgery's darkest period in history. While turning the lights back on at different times throughout May—like so many Thankful Villages after the Great War—ambulatory surgery centers nationwide resumed elective procedures for the first time in six to 10 weeks. As expected, the last ASCs to open were those in New York. COVID-19 decimated the Empire State with more than 354,370 infections and 28,000 deaths before surgeons there finally gowned up for daylong procedures again, joining their peers throughout the country.

"Our office opened this week and our surgery center will be open for elective cases next week (10 weeks after closing on March 10)," texted a very busy Eric Donnenfeld, MD, on May 21, with no time to talk on the phone

Dr. Donnenfeld, of OCLI Vision, operates at Island Eye Surgicenter in Westbury, New York. He's one of thousands of entrepreneur surgeons across the country who've spent countless hours bringing once-humming-then-closed ORs back to life, performing feats of resourcefulness and spontaneous planning that had never been previously attempted.

James Loden, MD

James Loden, MD, spent more hours than he wanted studying plans and logistics for a reopening—only to gain his biggest insights from diverse patient populations with varying needs.

Read on to find out how these surgeons crossed off the nearly mind-numbing restart checklists from four societies, coordinated staff efforts, planned safety protocols, re-triaged patients-in-waiting and completed numerous unexpected tasks, from the mundane to those of critical importance.

First Response: Lots of Prep

"How do you reopen an ASC and get back to seeing patients again?" Dr. Donnenfeld asks. "Our new mindset needs to focus on the most technologically advanced operation. It also has to be the safest operation intraocularly, minimizing any risk to our patients, their families, our staff and surgeons."

Dr. Donnenfeld urges every ASC to maintain a vigilant continuation of compliance with state requirements and other guidelines, reviewing dozens of recommendations for how to reopen and continue to operate.

Critical issues are covered on extensive checklists provided by the American Academy of Ophthalmology, the American Society of Cataract and Refractive Surgery and the Outpatient Ophthalmic Surgery Society (aao.org/practice-management/article/ophthalmic-asc-reopening-guidance), as well as the American

James Loden, MD

A new age of communication with hand signals and muffled voices dawned at the Loden iVision ASC on May 4, the first day of elective procedures at the Paris, Tennessee, Center in seven weeks.

College of Surgeons (facs.org/covid-19/clinical-guidance.)

"Some decisions are easy to make but some might be a little more difficult," he admits. "My suggestion is to put together an advisory board consisting of nursing, administration and doctors to decide on the best way to proceed on all issues. We've also relied on our colleagues in states where they've opened earlier to find out how they've handled various hurdles. For example, there's some debate about what type of mask should be worn. Consider the standard in most ORs. Some people have N-95 masks, which will filter out viruses, but most consider this unnecessary. The important point is that all doctors and nurses and patients should wear masks, and patients should wear masks under their drapes during surgery."

Removing a mask and gloves properly is also important to avoid contamination, he adds. "It's very easy to touch your face and and then remove your masks. You have to follow aggressive sterile technique when you do that. Aggressive hand-washing

Full protective gear is being put to good use for elective surgeries to guard against COVID-19 infections at the Loden iVision ASC.

is also important. And we're checking the temperature of all patients and staff and doctors when they come into the OR, on a regular basis. "We're asking all family members to wait in their cars, and we're going to keep the waiting room as empty as possible," he says. "We've removed chairs from the waiting room to make it impossible for people to sit next to each other, and we'll be repurposing the room as a transition area."

Dr. Donnenfeld says his group is resigned to facing "many more hurdles" in the months ahead. "We're going to need to maintain constant sterilization of all surfaces," says Dr. Donnenfeld, "and we have reduced our surgical volume by about 40 percent. We will be getting used to a new normal and then, once we get accustomed to the new flow in our ORs, we will begin to ramp up our ORs, hopefully to the same levels we had before."

Minimizing Patient Interactions

To minimize patients' personal contact with staff and surgeons in the office, Dr. Donnenfeld says OCLI has relied on telemedicine and minimized "touch services," encouraging patients to fill out forms online, for example. "We're triaging our patients based on need and the visual problems they're having. We've had thorough and continuing contact with our patients, which I think is very important." One challenge is that, in New York, patients need to undergo a physical exam by their general practitioners 30 days before surgery. As a result, a number of patients will need repeat exams before surgery, Dr. Donnenfeld notes.

"One of the controversial areas that we've been exploring is whether patients should be checked for COVID-19 infection when they come to see us," Dr. Donnenfeld says. "The advantage of having the patient checked is knowing that he or she is not infectious. The disadvantage is having to wait two or three days, potentially, for test results. The tests are mildly expensive and limited in sensitivity and specifity, so it's very common to have false negatives and false positives."

In Arizona, where Yuri McKee, MD, MS, is a corneal and refractive surgeon at East Valley Ophthalmology in Mesa, he says all patients are required to test negative for COVID-19 before elective surgery.

"So, with a negative test result, with the surgeon wearing a mask, and a judicious use of phacoemulsification energy, I think the risk of surgical-related viral transmission is quite low, but certainly not zero. The simple truth is: We can reduce, but not eliminate, the risk of virus transmission. Straightforward PPE rules should reduce the risk the most."

Dr. McKee is still weighing approaches to minimizing risk of infection while performing phacoemulsification. "I'll be wearing a surgical mask and dropping dilute Betadine on the cornea during the case, just as I typically do," he says. "If a plume evacuator is readily available I would't object to using it, but I think it's impractical to expect everyone to find a plume evacuator for phaco

surgery. Studies could be done to see how much tear-film aerosolization is caused by the phaco probe. Until more definitive evidence is presented, we'll need to do the best we can with the information that's known."

Dr. McKee points to one recent investigation by Bristol Eye Hospital in Bristol, United Kingdom, which found that the application of hydroxypropyl methylcellulose (HPMC) once every 60 seconds around the surgical wound during phacoemulsification eliminates visible aerosol. For a demonstration of the investigation, involving human cadaveric scleral models, go to the following link: youtube/8LGwI9LIYmU

On another front, he asks: "Should we be holding off on elective LASIK cases? Well, I'm not doing LASIK right now, but that's more because I've such a backlog of intraocular surgery that I can't be spending time on elective refractive surgery. At some point, we'll have to address the idea of viral transmission from the LASIK plume. For these cases, I probably would recommend an N-95 mask or even an industrial NIOSH VOC mask just to limit the chance of viral transmission from a LASIK plume."

Eric Donnenfeld, MD

Cataract surgeon Eric Donnenfeld, MD, resumed elective surgery at Island Eye Surgicenter in Westbury, New York, for the first time in 10 weeks on May 25.

Reduced Risks in Florida

Cataract and refractive surgeon Farrell "Toby" Tyson, MD, owner of TysonEye, which has multiple locations in Florida, including Bonita Springs and Cape Coral, says he isn't concerned about the risk of infection from aerosolization during phacoemulsification. "I don't phaco outside of the eye," he says. "Everybody wears masks, including the patient."

With less than 2,000 COVID-19 infections reported by May 4 in the counties where he practices, Dr. Tyson's practice resumed elective procedures on that date. The practice offers femtosecond cataract surgery, glaucoma surgery, custom wavefront LASIK, oculoplastic surgery and retinal care.

"Here we have two different types of patients," says Dr. Tyson. "One type thinks the threat of COVID-19 infection is overblown. They just want to get their cataracts done and they're not worried. On the other hand, you have patients who are in a high-risk category who are going to stay locked down until it's pretty safe. Everybody's been saying we're going to have a big boom in surgery cases now that we've opened back up, but I don't see that happening. It's going to be a slow startup."

Managing time-consuming protocols to reduce patient crowding and ensure safety, Dr. Tyson only operated at 25 percent of his usual capacity when he started. "Normally I do eight to 10 cases an hour in two operating rooms," he says. "Now, we have family members waiting in their cars, not the waiting room. With the decreased volume, we don't have that time pressure going on because we have fewer patients coming through. Of course, we're giving patients masks, and we do temperature checks before they come in for surgery. But we're not testing our patients and staff for COVID-19. What good would that do if they got infected between the time of a negative test and the time for surgery? And there have not been enough good tests around to use. As we get up to speed, I'm probably going to increase my volume and finally get it to where it has been. But I don't think things will get back to normal until October."

Admittedly less concerned about rampant infections because of the low incidence of COVID-19 in the towns where he practices, Dr. Tyson is also concerned about the health of his practice, which employs 85 people at six offices, including three surgeons and four optometrists. He says he was fortunate to receive a U.S. Paycheck Protection Program loan to pay for 75 percent of salaries. But he's paying the remaining 25 percent of the salaries out of pocket. He hopes that increased volume will put the practice on better financial foot-

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ing soon. "The good news is we are still fully staffed," he says. "I believe 70 to 80 percent of ophthalmologists have laid off staff. And that will not be a great position to be in when the patients come back. We haven't had it nearly as bad as New York and we also have a higher per capita elderly population. So that bodes well for us."

As a practice owner who has endured four major hurricanes, Dr. Tyson says his best protection is managing his practice conservatively. "I have believed in being debt-free, he says." "Our buildings are all paid off. That long-term conservative, fiscal policy of our practice has allowed us to weather this storm better than most."

Eric Donnenfeld, MD

The waiting room at Island Eye Surgicenter in Westbury, New York—idle for 10 weeks—will be kept nearly as empty as chairs are removed and it's converted into a transition room.

Know Your Patients

James Loden, MD, owner of Loden iVision Centers, which includes an ASC in Paris, Tennessee, and six offices in the state, has spent a lot of time at his desk while cut off from elective procedures, working on plans to stay in business during a 50-day shutdown. He reopened May 4, maximally meeting the safety needs of his patients and staff while developing strategies to recover lost surgical volume. For all of his calculations, however, he says he gained most of his insights on how to go from a survive to thrive mode by paying attention to his patients' regionally-flavored wants and needs. These traits reflect the rural and metropolitan patient populations that visit his offices in three counties.

"In the metropolitan area of Nashville, we see nothing but fear, uncertainty, people wearing masks everywhere," he says. "The challenge with them is to assure them it's safe to visit us and undergo procedures. We're following standard safety protocols for all patients. But in the rural areas, we have quite a bit of a different challenge. Hardly anyone in any of these areas is wearing a mask. All these patients want to know is why they couldn't just come in and get their cataract surgery done weeks ago, and, 'Why is the government ruining our economy?'

"We have to convince these patients and their families that we have to sacrifice some patient-centric accommodations. The families have to wait in their cars while we assess the patients under the awning outside the ASC, checking their temperatures. When checking them in, we mask everybody. Every employee is going to have an N-95 mask and eyewear. But many of the patients refuse to wear masks until we insist on it.

"We tell patients' families to keep their cell phones turned on so we can let them know when their loved ones are ready inside the ASC. But I'd say one-quarter of the elderly family members don't have cell phones in these rural areas. So this is another logistical problem—needing to free up staff to go out and get family members when the postop patients are ready to go home."

Dr. Loden, fully committed to safety, has put office furnishing into storage and replaced them with sturdy plastic chairs that are cleaned every time someone sits on one. "We have labeled each room according to protocols to make sure each room is sterile," he says. "All the knobs on the doors, the headrests, chin rests, arm rests, slit lamp, counter tops, computers and light switches have to be sanitized after every patient visit, so there are some throughput issues that can slow us down. But we need to keep the patients safe. And one thing I believe is that how we emerge from this crisis is going to depend on how well our employees perceive that we are protecting them as well. That's just as important."

Responding Appropriately

Dr. Loden has responded to the multiple challenges his practice faces with a mixed approach, including a web page that promotes both telemedicine and in-person visits. Virtual consultations spare patients a trip to the office when they're planning to undergo LASIK, which Dr. Loden's group has already begun performing, ahead of most practices.

As careful and accommodating as Loden iVision is with patients, such as gently escorting the elderly in and out of buildings, the practice also projects an undercurrent of promotion. A banner flashes upon first click on the practice's web page, proclaiming, "All locations are now OPEN!"

"We have three surgeons who've had a combined 35-percent reduction in volume, which is a huge financial hit to the practice," says Dr. Loden.

"I don't think people are factoring that in at other practices. You have to factor in a decrease in your clinic volume and in your ASC volume—if the patients show up. Can you be viable while reducing your business 30 percent long-term? We don't know the answer to that, and we're modeling it right now, just like a lot of other ASCs, no doubt." REVIEW

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Sterilizing Surgical Masks During a Crisis

Finding ways to make the most of essential equipment that's in limited supply calls for ingenuity. Here's an update.

Christopher Kent, Senior Editor

It's no secret that hospitals and other health-care clinics are short on personal protective equipment because of the COVID-19 pandemic. Out of necessity, organizations have now been forced to investigate different methods for sterilizing protective gear such as surgical masks that were designed and approved for single use only, thus allowing them to be used multiple times before disposal.

Because COVID-19 is an airborne pathogen, face masks such as the N-95 respirator are especially crucial for protecting health-care workers. For that reason, much attention has recently been paid to finding ways to eliminate or deactivate any virus on these masks without damaging the masks' functionality. (In an effort to facilitate this process, the U.S. Food and Drug Administration recently granted several emergency use authorizations to allow decontamination and reuse of this type of mask.)

Methods that have been tried to date include using ultraviolet light, bleach, ethylene oxide gas, dry heat, vaporized hydrogen peroxide and even microwave radiation. (The latter was judged unsuitable early on because it damaged the masks.) Currently, the alternatives that appear most feasible are UV light and some form of vaporized hydrogen peroxide. Each can be applied in different ways, with different advantages and limitations. Here, health-care professionals share what they've learned from working with these two options.

Exploring the Possibilities

Robert C. Cohenour, MD, a neurologist in practice for more than 40 years in Northridge, California, is the CEO of two large, multispecialty surgical centers that are part of a series of group practices. About 45 ophthalmologists use the ophthalmological surgical center. "We're adjacent to two hospitals in the San Fernando Valley, and part of the emergency service network in the community," he says. "We have arrangements with those hospitals to accept overflow patients, so we're not just doing elective cases."

Dr. Cohenour notes that surgical centers don't generally require N-95-grade masks. "We're using the N-95 masks now primarily in the operating room area, and for any nurse that feels that he or she needs to have a respirator mask," he explains. "Because of the pandemic, we're using them more routinely, in addition to safety shields in some situations. We had to start recycling the masks because we didn't have enough sources from which to buy them, and the cost was exorbitant, particularly at first. Luckily, a donor contributed a bunch of masks to each of our facilities."

Once the need to reuse the N-95 masks became clear, they began investigating ways to sterilize the masks with minimum damage to the masks' fit and filtration capacity. "We have a Sterrad sterilization system at one of our surgical centers," he says. "It uses a combination of gas and hydrogen peroxide; it's described as low-temperature sterilization, although it runs at about 160° Fahrenheit.

"The Sterrad system does sterilize effectively," he continues. "However, it has several practical disadvantages if you want to use it for sterilizing disposable surgical masks like the N-95. First, the process takes several hours. Second, the time required to run the process forces us to steril-

ize multiple masks or other PPE at the same time, leading us to be concerned about cross-contamination. Third, the system is very expensive compared to a UV-C light system; it cost about $25,000 when we installed it. Perhaps most important, in our experience it causes more damage to the N-95 masks than sterilization using UV-C light."

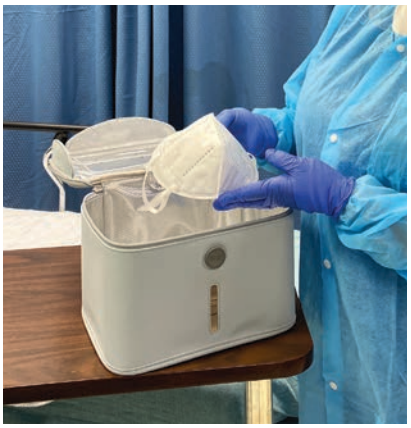
Dr. Cohenour says his practice is now using the 59S UVC-Portable UV Light Cleaner/Sterilizer Box P55 system, a small box with UV-C lights on all four of its internal sides. Masks are placed inside the box individually and irradiated for several minutes. "The multiple lights produce UV-C light throughout the container, not just on one side," he points out. "It's supposed to be a three-minute sterilization process, but we run it for 10 minutes as an additional safety precaution.

"The box is large enough to do five or 10 masks at once, but because it doesn't take long and we only have 31 employees here, we can sterilize one mask at a time and still get all of the masks sterilized every day," he continues. "The light doesn't disrupt the respirator filter or the metal stays that help the mask conform to the user's face."

Dr. Cohenour says the UV-C boxes are now used in both of their ASCs. "Our process is pretty straightforward," he says. "Everyone's mask has his or her name and the date first sterilized written on it. At the end of the day, each mask is sterilized in the UV-C box, and then placed in a paper bag with that person's name on it."

Lessons from Biocontainment

Michael Hartley, emergency manager for the University of Iowa hospitals and clinics and operations manager of their special pathogens unit, is well-acquainted with the issues surrounding decontamination. "Our biocontainment unit is a pod of four isolated rooms that have their own air-handling system," he explains. "Although the pod is secure and has all the features of a modern biocontainment facility, most days it's used as an intensive care unit taking care of trauma victims. If we need biocontainment, the unit is quickly converted to let us care for people carrying some of the most dangerous pathogens on the planet. Once those patients have been cared for, we have to turn that unit back into normal intensive-care rooms. That means we have to make sure those rooms are as aseptic, clean and disinfected as humanly possible."



Ultraviolet-C light has been proven to kill the coronavirus, given sufficient exposure. Here, a box containing multiple UV-C lamps is used to sterilize a surgical mask by irradiating it from all sides for 10 minutes.

Mr. Hartley has spent a lot of time searching for the safest and most effective ways to manage this. "A few years ago I ran across a technology called SteraMist, available from Tomi Environmental Solutions (Beverly Hills, California), that sterilizes with ionized hydrogen peroxide," he says. "Previously, we were using UV-C light for room sterilization. We'd purchased six very powerful UV robots that roll into a room and blast it with UV-C light. But we quickly realized that this approach has some limitations, given that UV light travels in a straight line; it doesn't go around corners, so areas in shadow might not be effectively sterilized.

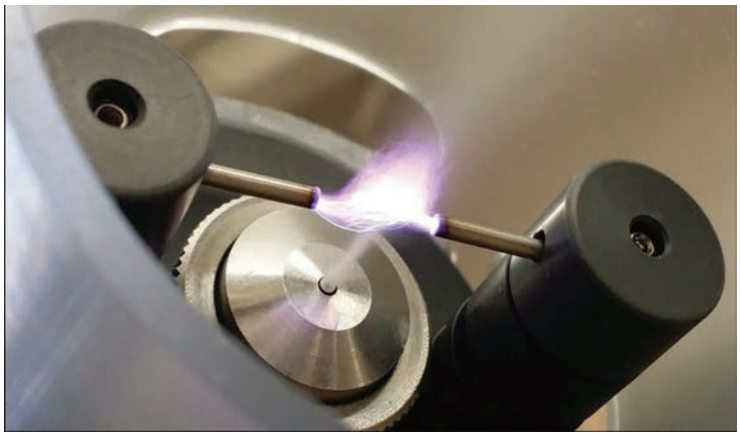
"I wanted something that would get into every nook and cranny of a room, without harming surfaces or objects or sensitive electronics," he continues. "Vaporized hydrogen peroxide looked interesting to me. However, some systems using this approach include antimicrobial additives such as silver in the vapor, and that concerned me. In addition, some of them use very high-concentration hydrogen peroxide. The hydrogen peroxide you buy in a drug store is about a 3% concentration. It's safe; you can swish it in your mouth. But some of these systems use concentrations as high as 35%. That's a hazardous material."

Mr. Hartley explains that the SteraMist devices position electrodes in front of a pinhole nozzle that shoots a high-pressure stream of 7.8% hydrogen peroxide. "The mist passes through a 17,000-volt cold-plasma electric arc," he says. "When the hydrogen peroxide mist hits the arc, the hydrogen peroxide molecules are split into hydroxyl radicals made up of one hydrogen and one oxygen atom. When these radicals hit the cell wall of a mold, virus, bacteria or fungus, they oxidize and destroy the cell wall, reportedly within about three seconds.

"We brought the SteraMist system in and tested it with help from our state hygienic public health laboratory," he continues. "It produced a six-log kill; that means more than 99.9999 percent of the spores we used as test organisms were killed. Other research we reviewed revealed no documented harm to sensitive electronic equipment or surfaces or materials. Ultimately, we bought the system for fogging the biocontainment rooms after special pathogen care."

Sterilizing Masks with Vapor

When the current crisis arose, Mr.



Vaporized hydrogen peroxide is effective against coronavirus, although it can be toxic at high concentrations. Above: The SteraMist device ionizes a lower-concentration hydrogen peroxide mist by passing it through a 17,000-volt electic arc; the resulting ions destroy bacteria and viruses without harming materials or electronics. Right: The device is used to mist surgical masks.

Hartley realized he might be able to use the same technology to make disposable items such as masks reusable. "As it turned out, the manufacturer of the SteraMist system had already developed a protocol for this for hospitals in Hong Kong," he says. "I decided to see if we could use it to disinfect masks such as N-95s on a large scale. To do this, we borrowed some logistical ideas from our friends at the University of Nebraska, who were already trying this using UV-C light.

"We had to be sure this process would work without harming the masks or reducing their ability to filter," he continues. "Working with a neighboring NIOSH-funded environmental health and safety laboratory on our campus, we were able to test the masks after treatment. The tests showed that the treatment caused negligible filtering degradation. However, the lab said we shouldn't use the process on a mask more than three or four times.

"It turned out there was a reason for this," he explains. "Many people don't realize that a key reason N-95 masks are so effective is that the material has an electrostatic charge, just like some furnace filters you can buy. When air is passing through the mask, it's filtered not only by the size of the holes through which it passes, but also by the electrostatic charge pulling particles out of the air. Because of that, the mask can be just as effective as a heavier mask, without being as thick. That makes them easier to breathe through than, for example, a homemade mask.

"This turned out to be relevant, because the SteraMist system ionizes the hydrogen peroxide by passing the mist through a powerful 17,000-volt electric arc," he says. "We realized that might be affecting the electrostatic charge of the mask material. So, we put greater distance between the device and the masks, and it made a difference; now we're able to sterilize the masks six times without noticeable degradation. Although we can't prove it, we hypothesize that the revised protocol doesn't interfere with the electrostatic charge of the mask."

Practical Considerations

Mr. Hartley explains that when they spray masks with the mist or fog, the sterilizing effect is basically instantaneous. "However, the masks are then moist," he notes. "They have to dry a little bit. We dry them in a special room that has a lot of air exchange, and the evaporating hydrogen peroxide is then vented to the outside. This takes about 20 minutes, so the entire process takes 45 minutes to an hour.

"With the current system we can do at least 1,200 masks a day," he says. "This allows us to get people's masks back to them the same day or the next day. We've done thousands, and we haven't reached our full processing capability yet."

Mr. Hartley admits that one practical problem with the SteraMist system is that it's relatively expensive. "Most of the vaporized hydrogen peroxide technologies out there have a pretty steep price tag," he says. "That's a problem right now because money is tight as a result of the crisis. That's why I think most hospitals are trying to find ways to sterilize masks using whatever sterilization technology they already have in-house. Some are trying to use the same sterilizers they use for surgical instruments; protocols have been developed for that. Many hospitals have already been using UV-C room-disinfecting devices, and you can purchase small devices that sterilize with UV-C light that are less expensive."

(Continued on page 61)

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The Pros and Cons of OCTA in Glaucoma

Sean McKinney, Senior Editor

This relatively new technology has some potential, but questions remain.

As David Huang, MD, PhD, celebrates the 30th birthday of the technological brainchild he helped create—optical coherence tomography—he's also pleased with the progress of its 6-year-old sibling, OCT angiography, which is coming of age in retinal care and blazing a trail of baby steps in the glaucoma space. "It's intriguing," says Dr. Huang, a professor of ophthalmology at the Oregon Health & Sciences University in Portland. Also a professor of biomedical engineering at the OHSU School of Medicine, Dr. Huang pauses before reflecting further on the potential for helping his colleagues use this emerging erythrocyte-counting scanning modality to diagnose glaucoma and monitor progression. "We still have a fair amount of progress to make on this, but it's already giving us meaningful new parameters to observe and measure for our glaucoma patients."

The question in many glaucoma experts' minds is when OCT-plus-angiography, or OCTA, will come of age.

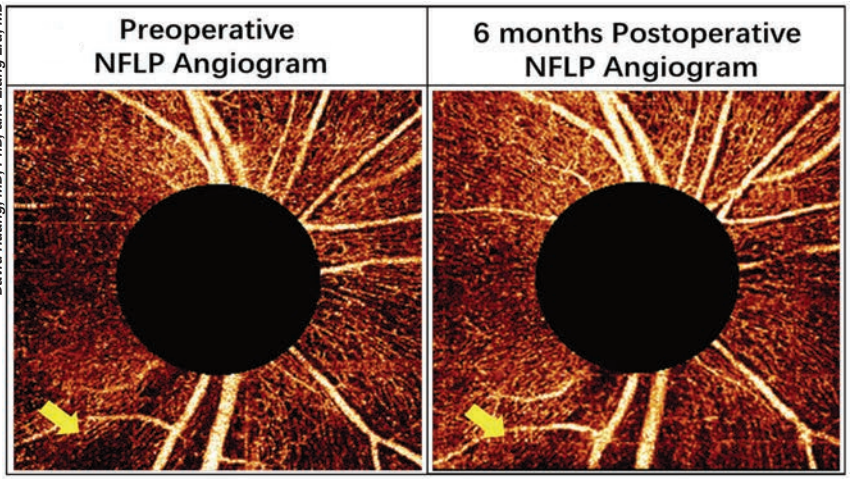
Still not widely used, even in many academic settings, the technology is short on supporting literature and lacks the robust normative data that's helped make the use of OCT an unofficial standard of care for both glaucoma and retinal specialists. Nonetheless, researchers working on limited OCTA studies have recently recorded two landmark findings on how the technology may someday be used in everyday practice as a tool that:

- could show that primary open angle glaucoma is not just caused by increased intraocular pressure, potentially opening a window for alternative treatments; [1] and
- may track progression in advanced primary open angle glaucoma in meaningful ways after OCT stops providing meaningful measurements of overly thinned retinal nerve fiber layer.[2]

In this report, researchers and glaucoma specialists talk about the promising future of OCTA, its current limitations and how much impact the technology could eventually have on the glaucoma care.

What is OCTA?

OCTA systems operate on one of two platforms: a spectral-domain system with an ~840-nm wavelength, used most often in glaucoma care;[3] or a swept-source OCTA with a longer ~1,050-nm wavelength that may allow for a deeper penetration into the choroid, a benefit that's mostly used in retinal care.[4] In 1990, Dr. Huang introduced OCT under the direction of James G. Fujimoto, PhD, his professor at the Massa-



David Huang, MD, PhD, and Liang Liu, MD

Figure 1. A mildly glaucomatous eye shows retinal perfusion recovery at six months post-trabeculectomy in 4.5-mm peripapillary OCTA scans (right). The overall nerve fiber layer plexus (NFLP) capillary density increased from 51 to 61 percent area. A significant perfusion recovery can be visualized in the inferotemporal region (arrow).

chusetts Institute of Technology. Their efforts led to a 1991 groundbreaking paper in which Dr. Huang and co-authors described the power and potential of this "noninvasive cross-sectional imaging in biological systems."[5]

Now that the use of OCT has evolved into a standard of care in the glaucoma and retina arenas, OCTA is gradually making a place for itself as as an add-on to OCT. The technology is currently available from OptoVue (through AngioVue, and on its Avanti widefield OCT platform), Zeiss (Cirrus HD-OCT with AngioPlex OCT), Heidelberg Engineering (Spectralis OCT Angiography Module) and Topcon, whose device (SS-OCT Angio powered by OCTARA) is still awaiting FDA approval.

The benefit of OCTA is that it compares sequential, cross-sectional OCT image frames at the same position, looking for signal fluctuations that indicate blood flow, according to Dr. Huang. He notes that the device uses this function to detect blood flow down to the capillary level, relying on a non-invasive scanning technique that mimics the invasive use of fluorescein angiography.

How OCTA Helps in Glaucoma

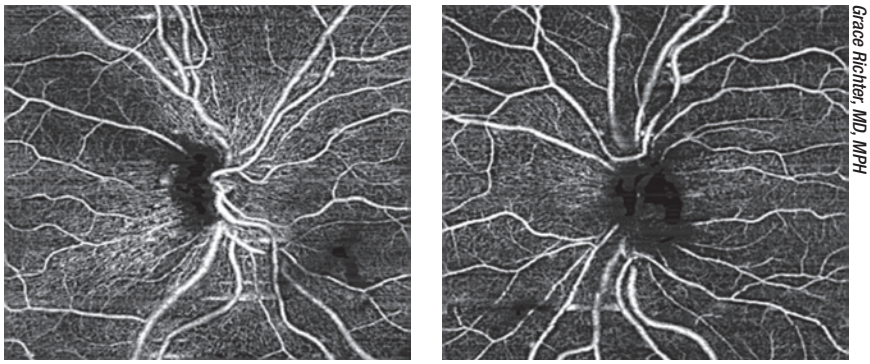
OCT angiography has been commercially available since September of 2015, five years after Dr. Huang's team began to help develop and test the technology. This has been made possible in recent years by the availability of faster OCT platforms, which allow for rapid, multiple scans of the same places in the eye, according to Dr. Huang. "It's worked amazingly well," he notes. "You can really get blood vessel contrast down to the capillary level. Our contribution has been to develop a very efficient method of detecting flow by comparing OCT signals, establishing a correlation that can increase signal-to-noise ratio, resulting in a flow detection capability that has made it possible to introduce OCT angiography for use by clinicians."

Dr. Huang says his team studied a number of areas of blood circulation in the retina and optic nerve head before finalizing the design. "Basically, we've established OCT angiography in the same location as the structured OCT image," he notes. "What we find in glaucoma is that the capillary density is decreased in the optic nerve head and peripapillary nerve fiber layer. We see RNFL thinning and, in the same area, reduced capillary density."

In the macula, he continues, reduced vessel density is present in the superficial vascular complex, a combination of the nerve fiber layer plexus and the ganglion nerve fiber layer plexus. "This is the same structure that's damaged by glaucoma," he says.[6]

Beyond IOP?

Robert N. Weinreb, MD, chair and distinguished professor of ophthalmology and bioengineering, and director of the Shiley Eye Institute at UC San Diego, says he and other researchers are studying where OCT fits into our



Grace Richter, MD, MPH

Figure 2. These are the two main types of qualitative defects seen in glaucoma patients when using OCTA. The image on the left demonstrates a large wedge defect in the presence of RNFL loss. The image on the right shows diffuse loss of the microvasculature, which is more obvious in advanced disease.

The One-Third Rule for Glaucoma Progression

Remember that not all glaucoma progression is structural, meaning OCT is of little use in certain cases.

- The ocular hypertension treatment study reported that 35 percent of patients had visual field loss but no sign of structural progression.[1]
- One study reported that 34 percent of all glaucoma-suspect converters demonstrated visual defects without structural progression.[2]

1. Kass MA , Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002 Jun;120:6:701-13
2. Medeiros F, Alencar LA, Linda M Zangwill L, et al. Prediction of functional loss in glaucoma from progressive optic disc damage. Arch Ophthalmol 2002;120:6:701-13.

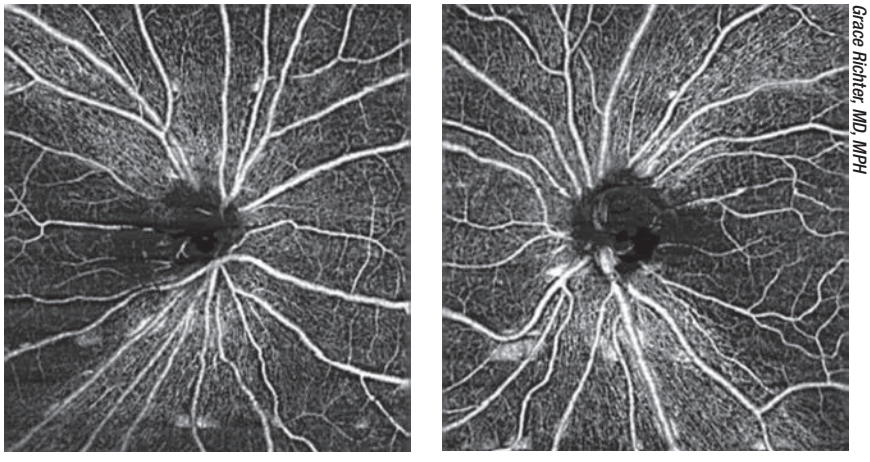
current paradigm of glaucoma management.

One study, published in *Ophthalmology* this past January, included 139 eyes (23 healthy eyes, 36 preperimetric glaucoma eyes, and 80 POAG eyes) of 94 patients who were seen over at least three visits.[1] Vessel density measured by OCTA and structural thickness measured by OCT were evaluated on the same 3-mm^2 GCC scan slab. Evaluation of associations between rates of thickness and vessel density showed significant rates of GCC thinning and macular vessel density decreases in all diagnostic groups, including comparable rates in healthy eyes and preperimetric glaucoma eyes. However, in the POAG group, more than two-thirds of the eyes showed faster macular vessel density decrease than GCC thinning.

The faster macular vessel density decrease rate was associated with worse glaucoma severity. IOP during follow-up significantly affected the rate of GCC thinning in all groups (all $p<0.05$) but notably showed no association with the rate of macular vessel density decrease. The researchers' conclusion was that macular vessel density is useful for evaluating glaucoma progression, particularly in more advanced disease.

What was left unsaid by the researchers, and remains open for exploration, is whether changes in macular vessel density in some individuals may reflect causes of glaucoma that are independent of IOP. "If confirmed in studies of longer duration and larger size, OCTA measurements may also be useful for evaluating glaucoma progression caused by factors other than intraocular pressure," says Dr. Weinreb. Noting that the duration of this study, up to 2.6 years in the POAG group, was longer than earlier studies, he says it provides a good foundation for hypothesis development. "Currently, intraocular pressure is the best-studied factor in what causes glaucoma," Dr. Weinreb notes. "There have not been accurate, reproducible, non-invasive technologies that can readily can assess vascular impairment or ischemia in the optic nerve. However, sensitive detection and monitoring of vessel density with OCTA might provide information about whether, in any individual, the IOP is the primary cause of damage, and whether loss of vessel density is merely a consequence of loss of neurovascular tissue. Alternatively, it might show whether real or observable loss of vessel density can lead to loss of neuronal tissue in some patients. Such an understanding might provide a basis for the development of new therapies, including those that protect the optic nerve independent of IOP."

Grace Richter, MD, MPH, assistant professor of clinical ophthalmology and acting director of the glaucoma service and glaucoma fellowship program at the University of Southern California's Roski Eye Institute, is also eager to find out to what extent vascular abnormalities may contribute to glaucoma. "Until now, we thought only intraocular pressure could cause the disease," she says. "But OCTA may help us learn more about normal-tension glaucoma. If there is non-pressure-related therapy that could potentially improve blood flow and prevent optic nerve damage, OCTA would be helpful in understanding the utility of those therapies and the extent to which vascular abnormalities contribute to glaucomatous damage."



Grace Richter, MD, MPH

Figure 3. After obtaining non-specific findings on OCT and Humphrey Visual Field findings suggestive of cecocentral defects OU, OCTA shows obvious papillomacular bundle defects suggestive of metabolic optic neuropathy, rather than glaucoma.

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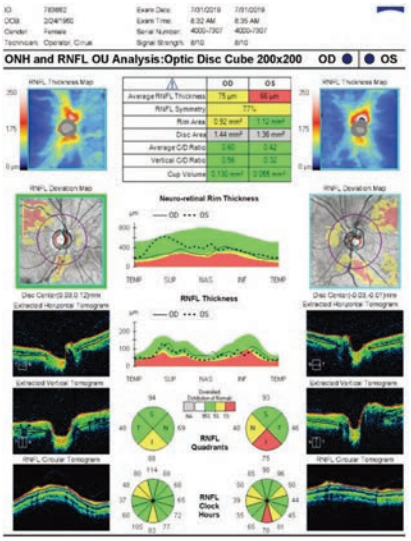
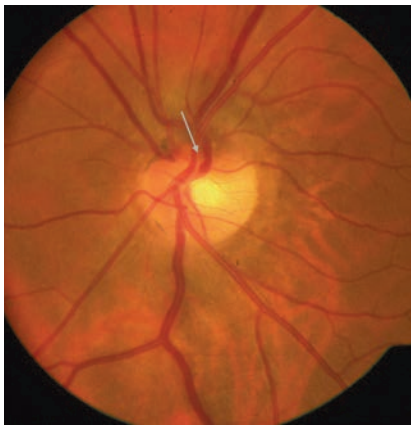
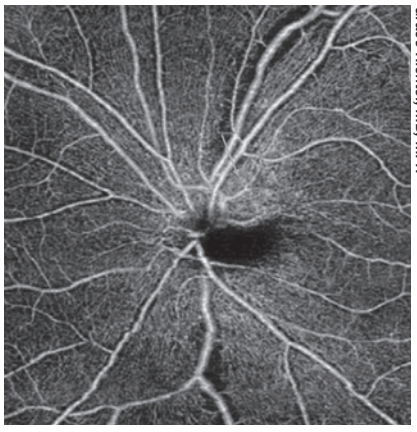






Grace Richter, MD, MPH

Figure 4. Despite the presence of a superior disc hemorrhage, OCT shows no local damage. OCTA, however, reveals an obvious superotemporal wedge defect in the area of the disc hemorrhage.

Late-stage Monitoring with OCTA

Another study involving Dr. Weinreb and his fellow researchers supports the use of OCTA for monitoring the late stages of glaucoma.[2] The study investigated the measurement floors and dynamic ranges of OCT and OCTA when monitoring glaucoma in 509 eyes of 38 healthy participants, 63 glaucoma suspects and 193 glaucoma patients. The relative vessel density measured by OCTA was compared to the circumpapillary retinal nerve fiber thickness, measured by OCT.

"In late-stage glaucoma, particularly when visual field mean deviations are very poor, worse than 14 decibels, OCTA's measurement of perifoveal vessel density is promising for monitoring advanced progression, because it doesn't have what's known as a detectable measurement floor," says Dr. Weinreb. "With OCT structural measurements, change is observed only to a certain level in advanced disease, at this detectable measurement floor. However, the floor is lower for OCTA. Using OCTA, one often can detect change in severe disease that can't be detected with structural OCT."

Does this mean that OCTA will always be better than structural OCT for detecting progression in advanced disease?

"Not necessarily," says Dr. Weinreb. "One possible limitation is the number of steps for detecting change. With structural change, you have more steps within the dynamic range than with OCTA. Only with longer duration studies and studies with greater numbers of patients will we know. With our current information, however, OCTA does appear to be a promising tool for detecting disease-related change in glaucomatous eyes with advanced disease. In contrast, we believe that, with our current technology, structural OCT, rather than OCTA measurements, may be more sensitive for detecting change in early glaucoma."

Even though most glaucoma specialists or other clinicians aren't routinely using OCTA for glaucoma management, Dr. Weinreb is guardedly optimistic on its future. "We're excited by the technology," he says. "Not only does it have application to glaucoma care, we believe it also could lead to novel therapies for glaucoma."

Monitoring Moderate Glaucoma?

Dr. Huang of OHSU also sees the potential for the use of OCTA for monitoring progression in moderate disease, not just the severe cases recent research seems to support. The nerve fiber layer also thins so much in moderate cases that OCT can barely help perceive further change, he points out.

"You can find measurements getting as low as 40 to 50 percent of the original reduced thickness that was identified in the patient," observes Dr. Huang. "The decreases become very small, and it's very difficult to gauge progression of the disease once the patient develops even moderate disease. On the other hand, with OCTA, the capillary density seems to continue to drop in moderate and severe glaucoma. Of course, we already have visual fields to measures changes at this point, but visual fields have relatively poor test-to-test reproducibility. It can take as many as seven to nine visual field tests to really get a significant progression rate measurement."

OCTA's greater precision in moderate and severe disease leads to the potential benefit of being able to detect progression earlier in these moderate and severe cases, says Dr. Huang.

"If you go from having 5 percent of nerve fiber layer left down to 3 percent, that's a huge change in your visual sensitivity, but in terms of thickness, that difference is very small and difficult to measure," he says. "With capillary density, you can get the reproducibil-

ity down to 3 percent. The meaningful contrast of the capillaries might be very useful to rely on in these moderate to severe cases, whereas visual fields, as I mentioned, can be terrible, quite noisy, in these cases. The capillary density we measure with OCT angiography is in the layer of the plexus that we're interested in, providing diagnostic usefulness. You get more repeatable measurements measured off of the capillary density, compared to the visual field sensitivity."[7]

Monitoring Treatment

Dr. Huang says OCTA can also help determine how well a treatment has worked—and can even show that some effects of glaucomatous damage can be reversible. "We've found that, in fact, there can be a tremendous pressure-lowering effect from trabeculectomy," he says. "We see visual fields that show that the treatment has proven effective. This finding tells us that that the ganglion cells were not really functioning; they were sick. They were not functioning because of that high pressure. But once that pressure was removed, they started functioning better. Of course, you would never find a neurologic fiber layer getting thicker following treatment. The structure doesn't change once the damage has been done. But the capillary density, we found, can actually improve after the trabeculectomy. (*See Figure 1.*)

"OCT angiography is also different from structural OCT in this respect: You can measure improvement in function," Dr. Huang continues. "As the function improvements occur, you can actually see the capillaries coming back. The metabolism recovers after trabeculectomy.

"Additionally, if you have a neuroprotective drug or aother drug that might improve ganglion cell function or ensure its survival, you might have a direct effect on IOP and it would be hard to measure with OCT if that drug was effective," he says. But this is one way to measure if such a treatment is working. This is because the perfusion has been increased. We're able to see this because this method of measuring change is very responsive to short-term changes, based on blood flow."

Not Ready for Prime Time?

Sarah H. Van Tassel, MD, co-director of the glaucoma service and director of the glaucoma fellowship at Weill Cornell Medicine in New York City, says she has not yet ventured into the OCTA domain for routine clinical care of her glaucoma patients.

"OCTA is still relatively new," she notes. "It's a noninvasive modality that has the advantage of offering qualitative and quantitative assessments of the vasculature within the retina and optic nerve. I think that it's an incredibly interesting time for research related to OCTA. I wouldn't want my lack of interest in doing OCTA clinically to be construed as a lack of interest in the OCTA research enterprise, because I think it's rapidly evolving. OCTA might prove to be advantageous in important areas. Evidence suggests that the measurement floor is lower in OCTA than in OCT and that it may be valuable for identifying patients who are at risk for rapid progression or who are rapidly progressing before we realize it when we're using visual fields or OCT. So I'm definitely excited about it."

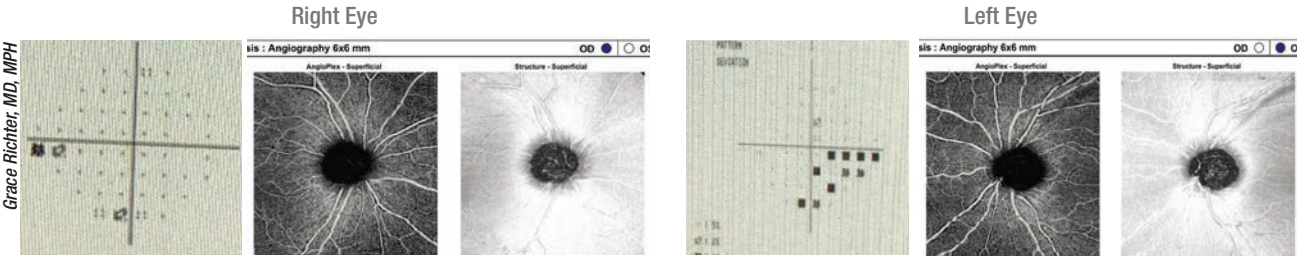
Despite Dr. Van Tassel's enthusiasm for OCTA's potential, she believes more development of the technology is needed to optimally enhance and support evaluation of the glaucomatous optic nerve and the glaucoma patient. "What we really need are easy-to-use, commercially available algorithms that are compared to normative data sets, enabling us to know what's normal and abnormal and what constitutes rapid change," she says. "To date, those kinds of clinical-support tools are not readily available when using OCTA."

Besides the need to acquire more normative data, Dr. Van Tassel says imaging artifacts associated with OCTA present a challenge. This is more so in OCTA than in OCT, according to the literature.[8,9]

"We will be forced to very closely interrogate the images for artifacts in OCTA, because artifact is one of the limitations and challenges associated with OCTA images," she says. "The retina literature has really gotten into the weeds on that topic.[10] A lot of reports point to patient motility and eye motility creating image artifact with OCTA, and challenges in trying to exactly duplicate the layer of the vasculature you're capturing each time you scan. It may be challenging to compare prior scans and future scans with normative data."

For the time being, Dr. Van Tassel relies on OCT, among other technologies, but she recommends a careful approach. When applying OCT to glaucoma care, for example, she notes that ophthalmologists in general tend to focus too much on the suggestive red and green colors included in scans. "Often, doctors aren't attuned to the nuances of scan results and to making sure the actual data and image acquisition are of sufficiently high enough quality to support clinical decision-making," she notes. "Remember that green means that a particular measurement is within the 90-percent range of normal compared to the eyes in the normative database. But the normative databases aren't perfect." She emphasizes that patients can have numeric data that fall in the normal range compared to the normative database and still have glaucoma. Conversely, patients can have numerical data outside the normal range but not have glaucoma.

Ophthalmologists are "good pattern recognizers," she continues. "I think that, because we like patterns, the colors on the maps become, in some respects, crutches, rather than support



Grace Richter, MD, MPH

Figure 5. OCTA shows a superotemporal defect in the left eye that correlates with the inferior nasal step seen on the visual field, a finding that was completely missed on the OCT scan.

tools, which is really what OCT and OCTA are meant to be.

"Quantifying progression is really difficult. How do you distinguish test-retest variability?" she continues. "How do you know if a patient is actually getting worse? In contrast to using visual field criteria, you really have no agreed-upon criteria for whether actual structural progression resulting from glaucoma is occurring. The guided progression analysis functionality of OCT is one tool that can be helpful."

Full Steam Ahead

Dr. Richter of the USC Roski Eye Institute has no reservations about using OCTA at this point. She performs one of these scans on virtually all of her patients after dilating them to produce better images, one or two times a year. She prefers to use 6 x 6-mm scans, the largest available, because larger optic nerve heads may not allow visualization of the surrounding peripapillary retina, an important component of an OCTA scan. She typically encounters two main types of qualitative findings: focal wedge defects and diffuse loss in advanced disease. (*Figure 2.*)

"There are cases when OCT is good enough for determining if a patient has glaucoma," she admits. "But I still try do an OCTA on every patient because I feel that, over time, it will be helpful longitudinally as I follow patients. We still don't know if that will be true at this point. I would say for the majority of cases, OCT is fine for making a diagnosis, but I've had a decent number of patients in which I've made the diagnosis of glaucoma based on OCTA, which is one of the reasons I try to get an OCTA scan on as many patients as I can. But keep in mind that I'm in an academic setting and this is my area of research, unlike many other ophthalmologists' settings and potential areas of research."

Some of Dr. Richter's successes in using OCTA for patient care have included the following:

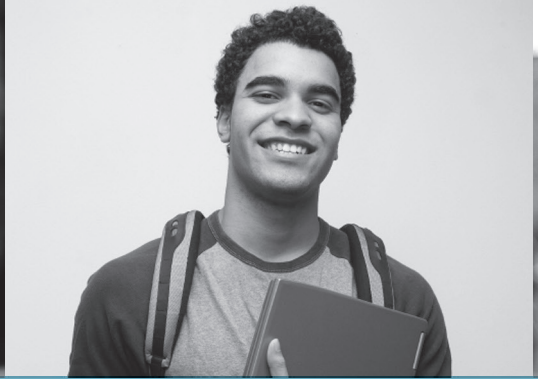
- A 70-year-old Caucasian woman, presenting for a second opinion on possible normal-tension glaucoma, had non-specific findings on OCT, and Humphrey Visual Field findings suggestive of cecocentral defects OU. OCTA showed obvious papillomacular bundle defects suggestive of metabolic optic neuropathy, rather than glaucoma (*Figure 3*).
- A 68-year-old African-American woman had open angles, IOP of 17 mmHg OD and 18 mmHg OS, normal central corneal thickness, a family history of POAG and full visual fields. She presented with a superior disc hemorrhage, but OCT showed no local damage. OCTA revealed an obvious superotemporal wedge defect in the area of the disc hemorrhage (*Figure 4*).
- A 31-year-old male presented with POAG and baseline IOPs of 14 mmHg OD and 15 mmHg OS. OCT showed left eye inferior thinning but no signs of the superior nerve damage expected from his inferior visual field defect in that eye. OCTA showed a superotemporal defect in the left eye that correlated with the inferior nasal step on the visual field. This was completely missed on the OCT scan (*Figure 5*).
- A 70-year-old Caucasian male had normal visual fields, open angles, an IOP of 12 mmHg, thin corneas and a nonspecific family history of glaucoma. OCTA showed an obvious wedge defect in the right eye, leading to a diagnosis of preperimetric POAG. Only a hint of the defect, non-diagnostic, had been found on the RNFL thickness map OD (*Figure 6*).

Better Study Needed

Despite her success when using OCTA on select patients, Dr. Richter notes that literature supporting the use of OCTA in practice needs to go beyond existing studies that focus on diagnostic accuracy.

"A lot of the literature supporting the use of OCTA in glaucoma has been focused on vessel density," she says. "For OCT, the literature often talks about the diagnostic accuracy of mean circumpapillary RNFL thickness. But most glaucoma specialists or general ophthalmologists who use OCT in glaucoma look beyond the summary mean of the RNFL thickness. There's a lot more data available from OCT. For example, looking in the focal quadrants and sectors, or looking at the RNFL thickness maps, can help with following glaucoma patients over time."

She believes that OCTA, similarly, can offer a lot more than diagnostic accuracy—more than a single summary parameter like vessel density of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Grace Richter, MD, MPH

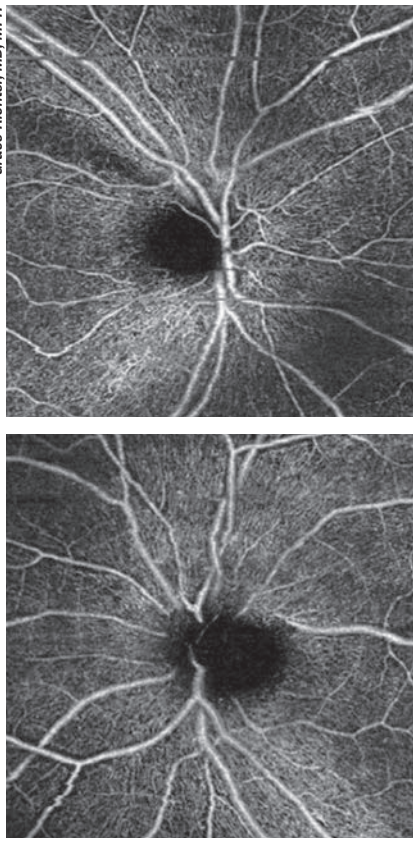

Figure 6. OCTA showed an obvious wedge defect in the right eye, leading to a diagnosis of preperimetric POAG. Only a hint of the defect, non diagnostic, had been found on the RNFL thickness map OD.

an OCTA image. "OCTA has actually helped me the most in the early diagnosis of glaucoma," she notes. "It has sometimes helped me with the question of whether a patient has glaucoma or not. OCTA can really help you identify focal characteristic effects on the microvasculature, which can be convincing enough to support a diagnosis of glaucoma. These are sometimes not so easy to see on OCT or during the clinical exam."

Broader Applications

Regarding whether general ophthalmologists should consider using OCTA, Dr. Richter says: "I think each practice has to weigh the pros and cons of acquiring OCT angiography. It provides an add-on to a lot of the current OCT devices and it's useful for a lot of retinal diseases. So I think most comprehensive ophthalmologists could find OCTA very helpful in numerous ways, not just when caring for glaucoma. Whether the cost is worth it depends on your patient demographics and what sort of practice you operate. If you want to practice with cutting-edge technology and really provide the highest level of technology for your patients, then OCTA will allow you to find the more nuanced manifestations of early glaucoma, once you learn how to detect those changes. At the same time, we're still learning a lot about of OCTA. So it may make sense to wait. For a more resource-limited setting, this technology might not be the priority. But it definitely does help in patient care."

A lot of glaucoma specialists say they aren't using OCTA at this point, but most expect that to change as more published literature supports the benefits of its use. OCT has existed for 30 years, they argue, so the literature supporting its use in detecting glaucoma and monitoring patients for progression is much more firmly established. "As we learn more about the qualitative benefits of OCTA, it will become more widely used," says Dr. Richter. "For example, for longitudinal studies to determine if OCTA can be helpful in detecting progression, there's very little literature because that takes time and we're very early on in the use of this technology."

For her part, Dr. Richter is making efforts to report on the qualitative findings of OCTA. "Hopefully it will be more practically-focused on how OCTA can be used to improve our care of patients," she says. "There are benefits you can get from OCTA that are not available in OCT. This is not just a matter of looking at a summary parameter such as the vessel density. You can also really look at the image qualitatively. I find it very helpful in new patients. I can find focal wedge defects in the microvasculature of the RNFL, and I've had several instances in which I saw a wedge defect that was consistent with glaucoma but that I really couldn't see in a clinical exam or on OCT."

Limitations of OCTA

Dr. Richter, acknowledging the limitations of motion artifact and sensitivity to media opacity when using OCTA, follows simple rules to prevent problems. "I avoid OCTA in a patient who can't sit comfortably enough for the length of the OCTA scan, which is approximately 10 to 20 seconds," she says. "The patient may be in a wheelchair, be very elderly or have a movement disorder. I also avoid OCTA if the patient has media opacities, such as a very prominent floater centrally, a cornea opacity or a dense cataract, for example."

Dr. Huang, whose decades of research and development work helped establish the giant footprint of OCT in glaucoma and retinal care, also acknowledges the shortcomings of OCTA. But he believes these shortcoming will be overcome in time.

"I think it will be a matter of the machines getting better," he says. "The software supporting the analytics will continue to get better, enabling you to be more sure of diagnosis and management decisions. Scan time will need to be efficient, and the imaging must continue to improve. And as so many doctors note, the advantages of using OCT angiography will also obviously need to be demonstrated in clinical trials and studies.

"I think, so far, the demonstrated benefits are most compelling for retinal specialists in areas such as neovascular age-related macular degeneration and diabetic retinopathy," Dr. Huang adds. "You can really use

(Continued on page 61)

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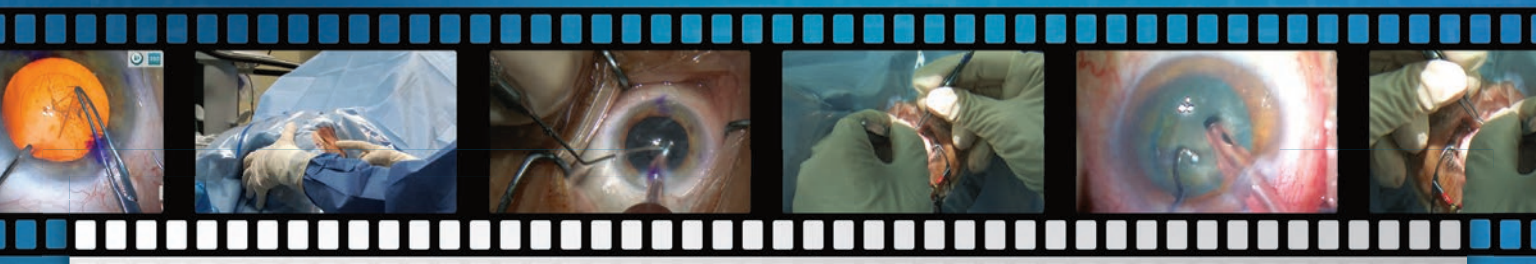

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Tips and Strategies for Tube Shunt Mastery

Christopher Kent, Senior Editor

Sugeons share their pearls for optimizing outcomes when implanting these devices.

Although topical drops remain the first-line treatment for most new glaucoma patients, surgery is often necessary to manage patients in need of major intraocular pressure reduction. For many years trabeculectomy has been the most popular approach in this situation, but that's slowly been changing.

Steven J. Gedde, MD, a professor of ophthalmology at Bascom Palmer Eye Institute in Miami, notes that the use of tube shunts for the surgical management of glaucoma has been growing in popularity. "Medicare claims data has shown a clear shift away from trabeculectomy and toward tube shunt surgery," he points out. "Also, a series of surveys of the American Glaucoma Society membership, starting back in 1996, has demonstrated that tube shunts are being selected as an alternative to trabeculectomy with increasing frequency.

"Historically, tube shunts were reserved for eyes felt to be at high risk for failure with trabeculectomy," he continues. "That included eyes that already had a failed trabeculectomy, eyes with extensive conjunctival scarring from prior surgeries and eyes with certain refractory glaucomas that tend to do poorly with traditional filtering surgery. The latter group includes eyes with neovascular glaucoma, uveitic glaucoma, iridocorneal endothelial syndrome, and epithelial and fibrous ingrowth; these eyes have been managed with tube shunt surgery for decades. Today, however, the shift has been toward the use of tube shunts in less-refractory patients. Some good emerging evidence even shows that these devices may be appropriate as an initial surgery—even in eyes at low risk of filtration failure."

Here, surgeons with extensive tube shunt experience share their insights and advice for getting the best outcomes when using these devices.

Choosing the Best Candidates

Like every approach to lowering IOP, the use of tube shunts can be problematic in certain eyes.

"I tend to avoid placing tube shunts in eyes that have very shallow anterior chambers or underlying corneal disease, because there's a higher risk of corneal edema with tube shunts in these eyes," says Dr. Gedde. "Corneal edema is usually related to the mechanical trauma that occurs if the tube touches the corneal endothelium, which can lead to progressive endothelial cell loss. In these types of patients I consider a surgical approach other than tube shunt surgery."

Brian Francis, MD, MS, a professor of ophthalmology in the glaucoma

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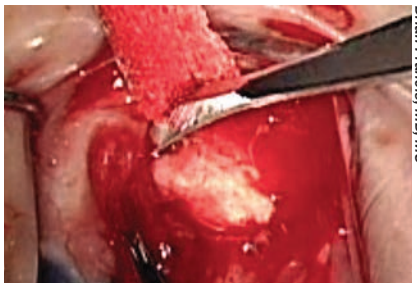
service and the Rupert and Gertrude Stieger Endowed Chair at the Doheny and Stein Eye Institutes, David Geffen School of Medicine, University of California Los Angeles, says he'd consider a tube shunt if the patient is at high risk for failure with other surgeries, such as trabeculectomy, or at high risk of infection or hypotony. "Tube shunts are also an option for patients who've failed to achieve adequate pressure reduction with MIGS procedures, or whose disease is so advanced that MIGS isn't seen as a good option," he says. "On the other hand, factors that make someone a poor candidate for a tube shunt include very poor ocular tissues, such as scarred conjunctiva; very thin conjunctiva; corneal endothelial disease; and a shallow anterior chamber, which can result in the tube causing endothelial cell loss."

Choosing the Right Shunt

Once you've decided a tube shunt is the best option for your patient, the next question is which shunt to implant. Dr. Gedde explains that tube shunts fall into two basic categories: valved and nonvalved. "Valved implants have a flow restrictor that limits aqueous outflow through the device if the intraocular pressure goes too low," he says. "The advantages of that design include a lower risk of hypotony, and the fact that the implant starts working immediately postop.

"In non-valved implants the major resistance to aqueous flow occurs across the fibrous capsule that develops around the endplate," he continues. "This capsule must be present before the tube is totally open and fully functioning; otherwise you'll have hypotony-related problems. For that reason, the surgeon has to restrict flow through the tube at the time of implantation to avoid hypotony in the early postop period."

Dr. Francis says the surgeon's choice is usually between a valved implant



Brian Francis, MD, MS

A scleral dissection being performed in a patient with thin, scarred conjunctiva undergoing tube implantation. The tube—typically with a patch graft placed over it—will be placed under this tissue. This preserves the conjunctiva and guards against erosion and exposure.

such as the Ahmed FP7 and nonvalved implants such as the Baerveldt 250 or 350, the Molteno, or the relatively new Ahmed ClearPath 250 and 350. "I use both valved and nonvalved shunts," he explains. "I tend to use a valved shunt in patients who have high pressure and need immediate pressure reduction but may not need pressure as low in the long term," he says. "Those patients are good candidates for the Ahmed FP7. If they need lower long-term pressure, I think non-valved implants such as the Baerveldt, Molteno or ClearPath work a little bit better."

"We know that eyes with uveitic glaucoma often have hyposecretion of aqueous humor, making them more prone to hypotony following glaucoma surgery," says Dr. Gedde. "A valved implant like the Ahmed FP7 helps to protect against that. A valved implant is also preferred in patients with markedly elevated IOP, when you need reliable pressure reduction immediately after surgery. However, in most cases I prefer nonvalved implants. There's good evidence that larger-size implants such as the Baerveldt 350 or the new ClearPath 350 provide a greater degree of pressure reduction. These are ideal for patients with advanced glaucoma, and for patients who are poorly tolerant of medical therapy—those in whom use of adjunctive medications is limited."

"In terms of choosing between the 250 and the 350 models, I base that choice on the severity of the glaucoma," says Dr. Francis. "In most cases I use a 250, but if a patient really needs a low pressure—which may be the case if the patient has low-tension glaucoma or advanced disease—I'll use a 350."

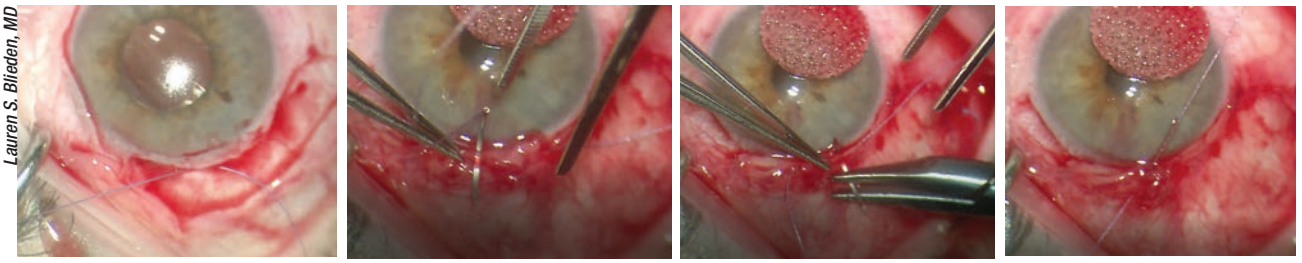
Lauren S. Blieden, MD, an associate clinical professor at the Alkek Eye Center, Cullen Eye Institute, Baylor College of Medicine, in Houston, says she likes to have all options available. "Some doctors only use one device," she notes. "I like to tailor my choice based on the patient's needs. For example, a neovascular patient needs to lower pressure very quickly, so an Ahmed FP7 is a perfect tube shunt in that scenario. The procedure is quick, patients tolerate it well and the pressure comes down quickly. This isn't the kind of patient who needs to end up with a pressure of 9 mmHg; you just need a pressure that's not 50 mmHg.

"Neovascular glaucoma patients may also do better with Ahmeds than Baerveldts," she continues. "Some data from the Ahmed vs. Baerveldt trial suggested this, as fewer patients progressed to NLP vision in the Ahmed group, although the study wasn't powered to check the statistical significance of this observed difference. My experience also has been that these patients tend to do better with the Ahmed FP7.

"In terms of uveitic glaucoma patients, everyone has a personal preference," she adds. "I like to use a Baerveldt 250 or ClearPath 250 with those patients, and I always use a ripcord suture to have control over when the tube opens."

Choosing the Plate Location

Another decision you need to make is where to place the plate on the globe. "You should almost always put the plate in the superior temporal quadrant, unless there's a compelling reason not to," says Dr. Francis. "Supero-



Above, left to right: Once a traction suture has been placed, it can also be used as a horizontal mattress suture during closure.

temporal placement lowers the risk of exposure, as well as the risk of the patient developing strabismus—which is something not every surgeon realizes. If that quadrant isn't available, then inferonasal is second-best. Superonasal and inferotemporal are generally the last locations to pick. However, if your patient is monocular, strabismus isn't an issue. In that situation, my second choice for placement of the primary tube, or for placing an additional tube—assuming superotemporal is unavailable—will be superonasal."

"When I'm considering tube shunt surgery, I look carefully for areas of scleral thinning preop," says Dr. Gedde. "Patients with certain rheumatological diseases and those who are highly myopic can be prone to scleral thinning. It usually appears as a bluish discoloration of the sclera, because the underlying choroid is visible. If I see thinning, I'll avoid those areas. Also, if a radial element has been placed during retinal detachment surgery, I avoid that region. Factors like these can influence our choice of where to place the plate."

Dr. Gedde adds that it matters how far posterior the plate is placed. "When I'm implanting a 350 Baerveldt, I use a caliper to measure 10 mm posterior to the limbus," he says. "I make a point of attaching the endplate at that location. It's important not to allow the endplate to be too anterior, crowding the rectus muscle insertion—at least with the Baerveldt 350, which is positioned underneath the adjacent rectus muscles. That could predispose the patient to having double vision."

Choosing the Tube Location

In most patients, the tube would be inserted into the anterior chamber, but other options are possible. For example, if the anterior chamber is problematic and the patient is pseudophakic, surgeons may consider placing the tube in the sulcus, posterior to the iris but anterior to the lens implant. Other options include:

• ***If the patient has peripheral anterior synechiae but the chamber is deep centrally, consider making a peripheral iridectomy.*** "Significant synechiae can prevent us from placing a tube in the usual position," notes Dr. Francis. "However, if you make a peripheral corneal incision and perform a peripheral iridectomy, you can insert the tube through the iridectomy."

• ***If the patient has no anterior chamber capacity or has existing corneal disease, consider putting the tube in the pars plana.*** "This might be the best option in this situation," notes Dr. Francis. "However, this will only work if you perform a vitrectomy, and the vitrectomy has to be very complete. Often, when someone has had a previous vitrectomy, it's just a core vitrectomy; the vitreous face and anterior peripheral vitreous are still present, so the tube can still become blocked with vitreous. Putting the tube a little farther in may help to clear the vitreous skirt, but the tube can still get blocked. And even if blockage doesn't occur right away, the remaining vitreous can liquify over time and end up getting into the tube at a later date.

"This option also is somewhat problematic because you won't be able to see the tube as easily, so you can't tell if it's blocked or open," he adds. "Implanting the tube in this way adds a layer of complexity to the workings of the tube, and to the exam required, but for many patients it's a great procedure."

• ***If an eye has silicone oil inside, put the tube in an inferior quadrant.*** "This helps in case the silicone oil migrates into the anterior chamber," explains Dr. Gedde. "Oil tends to float up, superiorly, which could lead to a problem if you put the tube in a superior location. The oil might drain through the tube or obstruct it."

Inserting the Tube

Dr. Francis notes that there are several ways to insert the tube. "You can tunnel through the sclera or put it in at the limbus," he says. "Tunneling works pretty well, but the longer your tunnel, the more the tube will tend to angle anteriorly towards the cornea, and that can be a problem. You don't want the tube touching the cornea, or even near the cornea. Finally, however you insert the tube, make sure it's well-covered, whether it's through a scleral flap or a patch graft or through tunneling."

• ***Consider creating a fornix-based conjunctival flap rather than a limbus-based flap.*** "Either way is acceptable, but I find that a fornix-based flap provides better exposure when placing the implant and inserting the tube," says Dr. Gedde.

• ***If the conjunctiva is scarred, consider making a superficial scleral flap.*** "Many surgeons are afraid to

implant a tube if there's scarring of the conjunctiva or very thin tissue in the preferred quadrant near the limbus," notes Dr. Francis. "However, you can still put the tube in that quadrant. If the conjunctiva is thin and atrophic and scarred, instead of trying to lift it up, you can make a superficial scleral flap—basically, a scleral dissection. That will get you to the limbus without disrupting the conjunctiva at all. Then you can put your tube in, put the patch graft on then put the conjunctiva down with a superficial or episcleral dissection. This actually works quite well."

• ***If the patient has a failed trabeculectomy at 12 o'clock or a little bit temporal to that, consider putting the tube through the existing scleral flap.*** "In this situation the globe has a tunnel in the sclera underneath the previous scleral flap and an existing peripheral iridectomy," Dr. Francis points out. "That allows you to enter the anterior chamber more posteriorly, away from the cornea. If you're able to enter more posteriorly, at the level of the iris, you're not going to hit the iris because there's an iridectomy there. You can simply put the tube through the iridectomy."

• ***Use an inked needle tip to mark your tube entry location.*** "I always mark the tip of the 23-ga. needle with a surgical skin marker," says Dr. Blieden. "When it enters the sclera it leaves a little ink mark, so you know exactly where your scleral entry site is when you go to insert the tube shunt. Sometimes I'll do that while leaving the needle on a syringe of viscoelastic or BSS, in case I also need to re-inflate the chamber to help place the tube."

• ***Use a guide wire to make it easy to insert the tube.*** Dr. Blieden says she came up with this strategy in the OR one day when she was having a particularly difficult time getting the tube into the correct position in the sulcus. "Sometimes it's very challenging to reposition an existing tube, or even get a primary tube to go where you want it to, whether it's above or below the iris," she explains. "Using this strategy makes it easy to get the tube where you want it.

"First, use a side-port blade, or the 23-gauge needle you've used to create the tube track, to make a small corneal paracentesis across from where you're trying to do your tube entry," she says. "If necessary, you can inflate the anterior chamber with viscoelastic. Then, take a piece of 3-0 or 4-0 prolene suture and insert it through that paracentesis.

"Next, insert a pair of disposable 27- or 25-gauge Maxgrip retina forceps through the track that you've created for the tube," she continues. "This is much easier than getting the tube itself into the correct track. Once the forceps is in the anterior chamber (or sulcus), use it to grab the prolene you inserted across the eye and pull it out through the planned tube track. The prolene suture then becomes a guide wire.

"Thread the tube over the prolene and then gently push the tube into the correct position, following the guide wire," she concludes. "Once the tube is inserted, you can pull the prolene out through the paracentesis and remove the viscoelastic, if appropriate. This has quickly become my favorite way to move a tube into the sulcus, or reposition a tube in the eye."

Intraoperative Tips

Other strategies for success include:

• ***When a patient is at high risk of hypotony, consider doing a staged tube procedure.*** Doing a staged tube means putting in the plate and waiting for the capsule to encapsulate before inserting the tube," explains Dr. Francis. "Six weeks to two months later, you put the tube in the eye." He points out that it's good to try to identify patients at higher risk of hypotony ahead of time. "Patients at the greatest risk of hypotony are generally older," he

notes. "They're vasculopaths with vascular disease and brittle blood vessels. With these patients, a staged procedure may be safest.

"Alternatively," he adds, "you can insert the tube and tie it closed, and then bring the patient back at five weeks and open the ligature in the clinic using laser suture lysis."

• ***Place your traction suture strategically.*** Dr. Blieden says she uses her 7-0 vicryl suture for corneal traction, but places it in the far peripheral cornea, aligned with the center of the limbal peritomy. "Doing this allows me to convert the traction suture into a horizontal mattress suture to close the central part of the incision at the end of the case," she explains. "Many surgeons use a corneal traction suture to get exposure for the tube shunt, but I place it very peripheral—almost into the sclera. Sometimes, if the cornea is tenuous because of existing pathology or a transplant, it's easier to first open the limbal peritomy until you get to bare sclera, and then place the traction suture at the corneoscleral juncture. That way, if the patient has had a corneal transplant or other corneal issue, you're not insulting the cornea more.

"Next, I put the traction suture on a locking needle holder," she continues. "I use a temporal Lieberman speculum because it has posts, so I can hook the suture around the posts. With the weight of the locking needle holder, that does a great job of holding the globe in place and allows me to manipulate the globe as needed. Then, when it's time to finish up, I convert it into a horizontal mattress suture to close the center part of the peritomy." *(See example, p. 40.)*

"I always use a traction suture placed at the limbus, in the quadrant in which I'm placing the implant," says Dr. Gedde. "That's very useful for rotating the eye to improve surgical exposure during the procedure. Then, I use that same traction suture at the end of the operation in the conjunctival closure."

Intraocular Pressure and Capsule Thickness

"The two major determinants of the final pressure achieved after tube shunt surgery are the total surface area of the capsule around the endplate and the thickness of the capsule," explains Steven J. Gedde, MD, a professor of ophthalmology at Bascom Palmer Eye Institute in Miami. "In terms of the first factor, it seems logical to assume that an implant with an endplate that has a larger surface area will produce a larger area of encapsulation around the plate and lower pressures.

"The other determinant of the final pressure is the thickness of the capsule," he continues. "Some patients have a strong healing response and generate a thick capsule. Unfortunately, the pressure reduction is less in those patients. Most of these patients need some adjunctive medical therapy after tube shunt surgery to reach the desired level of pressure.

"Some surgeons have tried applying mitomycin-C in the area of the endplate intraoperatively, to see if that might help modulate wound healing and create a thinner capsule," he adds. "So far, studies seem to indicate that this approach doesn't work well.[2,3] However, the Ahmed with Mitomycin-C Comparison (AMC) Study led by Dr. Ying Han at UCSF is evaluating intraoperative application and postoperative injections of mitomycin-C in the area of the endplate. Some early data suggests that this may be helpful in obtaining better pressures, with less need for adjunctive medical therapy."

—CK

• ***If the tissue is fragile and falling apart, start the closure posteriorly, toward the muscle insertion.*** "This is a strategy I learned from Dr. Gedde," explains Dr. Blieden. "When it's time to close a relaxing incision, if the anterior tissue near the limbus isn't healthy or substantial, start the closure posteriorly towards the muscle insertion, not at the limbus. This works because as you walk the tissue forward, you always end up with more tissue at the end of the closure."

• ***Monitor carefully for postop complications.*** "These include complications such as erosion of the tube, double vision, corneal edema, choroidal effusion and shallowing of the anterior chamber," says Dr. Gedde. "You need to be vigilant about monitoring for these complications. If they develop, early recognition is important so that appropriate treatment can be started."

Controlling Pressure Pre-opening

When implanting a non-valved device, most surgeons tie a vicryl suture around the tube to close it for several weeks while the healing response causes a capsule to form around the plate. By the time the suture releases, the capsule has formed and acts as a flow restrictor.

Since this process takes several weeks, a key decision for the surgeon is how to control the pressure during the time it takes for the capsule to form and the vicryl suture to open up. Some surgeons put fenestrations in the tube to allow a small amount of flow; others may choose to do another procedure at the same time, such as endoscopic cyclophotocoagulation or an angle-based MIGS procedure. Some create a ripcord suture that will allow them to open the tube at a time of their choosing.

Surgeons offer these suggestions:

• ***Do a MIGS procedure at the same time.*** "If I'm putting in a non-valved implant, and I need to get the pressure down in the short term, I'll consider doing a MIGS procedure at the same time," says Dr. Francis. "Usually it's a goniotomy, because you're generally not putting in MIGS

implants unless you're doing cataract surgery. Doing this at the same time may help control the pressure for the first six weeks."

• ***Consider creating an "orphan trabeculectomy."*** "If the patient doesn't have an existing trabeculectomy," says Dr. Francis, "you can make a new one next to the tube without using mitomycin-C, with the expectation that it will fail. By the time it fails the tube will be open and functional, and you will have managed the pressure during the interim."

• ***If the patient already has a failed trabeculectomy, reopen part of the trabeculectomy flap without using mitomycin-C.*** "Doing this will bring the pressure down," explains Dr. Francis. "Over time, that flap will scar down again because you didn't use mitomycin, but by then the tube will be open. I call that an 'orphan trabeculectomy revision.' It's a nice option, because the flap already exists.

"Reopening it is similar to a needling procedure," he adds. "I generally use an MVR or side-port blade to tunnel under the flap and open it again. However, you have to be careful not to open up the entire flap, because you'll get too much outflow and cause hypotony. I generally try to open up just half of the flap and then check the flow."

• ***Don't wait to adjust the patient's glaucoma medications.*** Dr. Francis suggests tapering the patient's glaucoma medications postop. "If the tube suddenly opens up, the eye may become hypotonous," he says. "At the very least, you don't want the patient to be on maximum aqueous suppressants during that time. If that happens, most eyes will recover, but some eyes won't; the result can be a flat chamber, choroidal hemorrhages and choroidal effusions."

Dr. Gedde notes that some recent evidence suggests that adding medical therapy earlier may reduce the chance of a hypertensive phase, which is common after tube shunt surgery.[1] "Treating that with medical therapy may reduce the magnitude and duration of the hypertensive phase and improve long-term pressure control," he says.

Dr. Blieden agrees that when implanting the Ahmed FP7, early aqueous suppression can help to blunt the hypertensive phase. "A hypertensive phase is fairly common with these implants," she says. "So, as soon as the patient gets to double-digit pressure I'll add in a little bit of an aqueous suppressant. I've had a lot of success with this approach."

Opening the Tube Yourself

In some cases, surgeons prefer to control when the tube opens, with the obvious advantage that any unwanted effects are more easily monitored.

Dr. Gedde notes that if you choose to open a nonvalved tube yourself, you should wait at least one month. "When I'm placing a nonvalved implant, I use 7-0 vicryl to temporarily restrict flow through the device," he says. "That suture reliably dissolves five or six weeks after surgery, which is enough time to allow a capsule to form around the endplate. But if you prefer to control the time of tube opening, you can use a laser to lyse the suture. If you do, wait at least one month to make sure the capsule has fully formed around the endplate."

When a uveitic glaucoma patient receives a nonvalved shunt, Dr. Blieden suggests leaving a permanent ripcord in place for as long as possible. "Uveitic patient outcomes are very unpredictable," she notes. "After I implant a Baerveldt or ClearPath 250, I tie off the tube around a 3-0 prolene ripcord and leave it there for as long as humanly possible.

"Some of these patients are impossible to control with medications, but after I put in the tube—still tied shut—their pressure normalizes," she continues. "In some cases, four years after the surgery I still haven't needed

to open the ripcord. I can't explain this, but it scares me to think that if I'd put in a valved tube, or a nonvalved tube without the ripcord, I would have been dealing with severe hypotony. So, I like to have the control of a ripcord in my uveitic patients. I typically advise doctors to resist the impulse to open it early. Wait it out. I won't open a uveitic tube before eight weeks, even if the pressure is in the 30s.

"With these patients, some surgeons might choose to do a staged Baerveldt implantation, where you have to go in and reopen that quadrant of the conjunctiva," she notes. "However, with this ripcord approach you can just cut down and pull the ripcord. You can do a scleral cutdown at the same time, if you need to.

"I use the same approach with my very old patients," she adds. "If I'm worried about the patient, I want to make sure I'm controlling how and when the tube opens."

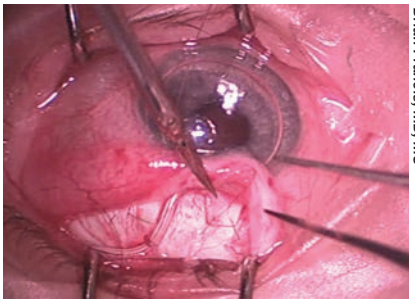
If a Primary Shunt Fails

If a tube shunt has already been implanted but the pressure-lowering that results is insufficient, the surgeon will have to decide what to do next.

One option is to add a second shunt. Dr. Francis says that if he decides to do this, in most patients, he'll put the second tube in the inferonasal quadrant. "However, if the patient is monocular I'd place it in the superior nasal quadrant," he says.

Of course, adding a second shunt means placing additional hardware on the eye, so most surgeons are careful to consider other options first. Those options include:

• ***Try cyclophotocoagulation.*** "Typically, if a patient has an Ahmed FP7 valve, which is a small implant, instead of adding a second shunt I'll try cyclophotocoagulation first, whether it's a micropulse or ECP," says Dr. Francis. "However, you have to avoid creating hypotony, which could happen if both the tube and your aqueous reduction procedure work well. Don't be overly aggressive with the cyclophotocoagulation."



Brian Francis, MD, MS

An orphan trabeculectomy has been created next to a Baerveldt tube in order to control intraocular pressure until the nonvalved tube opens.

Dr. Blieden says that in most cases she opts to perform an adjunctive cyclodestructive procedure instead of placing another shunt. "I may add a second shunt if the patient is young and phakic," she says, "but most of the time, if the first shunt fails, I opt for doing secondary cyclophotocoagulation."

• ***If the primary tube is valved, try replacing it with a nonvalved tube.*** "If a small amount of cyclophotocoagulation fails to get us to the desired target with an Ahmed FP7," says Dr. Francis, "I'll take the Ahmed out and put in a nonvalved Baerveldt or Ahmed ClearPath, because I think those work better in the long term. That avoids the need for another tube in another quadrant. If the patient already has a nonvalved Baerveldt, Molteno or ClearPath, then I'll go ahead and try micropulse or ECP. If that fails, then I'll put in a second tube."

Dr. Francis points out that switching the tube can also work in the opposite situation. "If the patient has a Baerveldt and the pressure's too low, which we sometimes see in uveitic glaucoma or neovascular glaucoma, you can take out the Baerveldt and put in an Ahmed FP7," he says. "That generally will prevent hypotony while still controlling the pressure."

Dr. Blieden says she'll only consider switching out a shunt if the current one has become a major problem. "I'll only resort to that if the shunt has eroded, or the patient is hypotonous," she explains. "If it's just an issue with controlling the pressure, I leave it alone and use other options to control the pressure."

• ***Try to revise the primary shunt capsule.*** "Some surgeons suggest revising the original shunt—for example, excising the capsule around the endplate in hopes that when the new one forms it will be thinner," notes Dr. Gedde. "However, in my experience, if the patient formed a thick capsule to begin with, it's unlikely the new one will be different. I generally leave the original shunt alone, as long as it's not obstructed. In my experience, if it's working but not lowering pressure adequately, the best options are putting another shunt in a different quadrant or doing cyclophotocoagulation."

Dr. Gedde adds that it isn't yet clear what the preferred surgical approach should be when a tube shunt fails. He's an investigator in the American Glaucoma Society's Second Aqueous Shunt Implant Versus Transscleral Cyclophotocoagulation Study (ASSISTS), a multicenter randomized clinical trial comparing cyclophotocoagulation and second tube shunt placement after primary tube shunt failure. "Hopefully, this trial will provide information to guide surgical decision making in the future," he says. REVIEW

Drs. Gedde and Blieden report no relevant financial ties to any product mentioned. Dr. Francis is a consultant for New World Medical, Endo Optiks and Iridex.

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Managing Dry Eye Postop Begins Preop

Michelle Stephenson, Contributing Editor

All surgical patients should be assessed for dry eye, say these ophthalmologists.

Dry-eye disease can reduce visual quality and adversely affect refractive measurements before cataract and refractive surgery. Additionally, ocular surgery can exacerbate or induce dry eye, which can lead to worsened vision, increased symptoms and dissatisfied patients. Because of this, surgeons say there are steps you can take pre- and postop to minimize the effect of dry eye on your surgical outcomes. To learn how they approach the problem, read on.

An Insidious Problem

"In patients who are cataract surgery age—60 to 90 years old—two-thirds to three-quarters of them are asymptomatic and have ocular surface disease," says Francis Mah, MD, who is in practice in La Jolla, California. "So, they don't even know that they have it. A lot of these patients think that it is a normal part of the aging process, like getting gray hair and wrinkles. It has been shown that, especially in the cataract surgery age group, dry eye is very prevalent and is often asymptomatic. We need to be looking for it even if they are not complaining about it."

He adds that dry eye can affect preoperative measurements. "Before cataract surgery, we are doing biometry and measuring keratometry. It is well-known that dry eye skews biometry and keratometry measurements," Dr. Mah says. "The same goes for refraction before refractive surgery. Obviously, this can have a huge impact on our surgical outcomes. Sometimes, you get a refractive surprise because of preoperative dry eye."

Besides less than optimal visual acuity, dry eye can cause postoperative fluctuation in vision and foreign body sensation. "Fluctuation in vision can be anything from blurred edges or blurry images to just overall reduction in vision," notes Dr. Mah. "Patients may also complain of foreign body sensation or burning."

According to John Sheppard, MD, of Norfolk, Virginia, there are two key issues with dry eye.[1] "One is that you may not be able to assess the proper target for your surgical intervention if the patient has ocular surface disease that impacts the topography and the refractive error in the eye," he says. "Two, after surgery, untreated ocular surface disease may worsen the recovery and significantly increase the risk of complications, including, rarely, infectious keratitis or conjunctivitis."

This article has no commercial sponsorship.

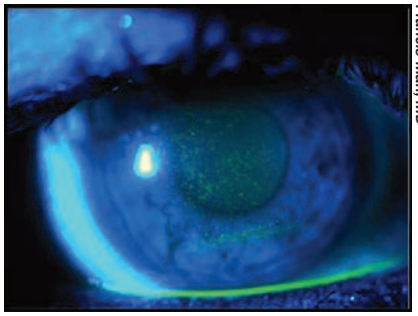
ASCRS OSD Algorithm

Dr. Mah is the chair of the American Society of Cataract and Refractive Surgery's cornea clinical committee, which recently published a paper in the *Journal of Cataract and Refractive Surgery* that described an algorithm surgeons can use to prepare their patients for cataract and refractive surgery.[2]

Surgeons should be looking for dry eye in every surgical patient, says Dr. Mah. "The ASCRS corneal clinical committee has been trying to educate people on looking for dry-eye disease, and ocular surface disease in general, so that outcomes will be better and patients will be happier," he explains.

Part 1 of the algorithm is a novel preoperative ocular surface disease questionnaire for all patients who are undergoing cataract or refractive surgery. Patients typically fill out the questionnaire before they see their surgeon. "It's a very simple questionnaire," Dr. Mah explains. "Because the SPEED questionnaire for dry eyes isn't proprietary, the ASCRS corneal clinical committee altered it a little bit for our preoperative surgical patients and included some personality questions, which help identify appropriate patients for premium cataract and refractive surgery. Obviously, LASIK patients are premium patients just by their nature. We also ask patients if they are experiencing any dry-eye symptoms. If the SPEED questionnaire is positive or if the patient reports any dry-eye symptoms, then he or she has stage 1 dry eye and dry-eye testing—depending on which tests—can be reimbursed," Dr. Mah explains.

Part 2 of the algorithm is the clinical examination, which includes the look, lift, pull and push examination.[1] The algorithm recommends looking at the blink quality and quantity and examining the eyelids. The surgeon should also be looking for signs of anterior and posterior blepharitis and looking at the interpalpebral ocular surface for signs of conjunctival injection, follicles and papillae, discharge and mucus, concretions, conjunctivochalasis, pingueculae, pterygia, conjunctival scarring and symblepharon.[1] Also, examine the interpalpebral cornea for any surface abnormality. Then, lift and pull out the upper eyelid, which is an often overlooked part of the ocular surface examination. Finally, push on the lower lid margin, which expresses the meibomian glands, and assess the quality, quantity and flow of the meibum. Vital-dye staining is also important to assess tear-film stability, experts say.



Francis Mah, MD

Fluorescein staining helps make the diagnosis in part 2 of ASCRS' algorithm.

There are many ways to test for dry eye, and some of them are reimbursed. Dr. Mah says that osmolarity testing by TearLab and MMP-9 testing are both reimbursed if a patient has a positive questionnaire or is reporting symptoms. "Other things like meibography and tear assessment by interferometry may not be reimbursed," he cautions. "Essentially, the next step, regardless of whether the patient says yes or no to any of the questions on the questionnaire, is to do some sort of dry-eye testing. This may just be clinical testing, but that testing can be enhanced with some of the point-of-service tests that are now available. Specifically, in addition to looking at the tear film for staining with vital dyes, I look at the tear meniscus, the superior conjunctiva, and the nasal, temporal and inferior conjunctiva for lissamine green staining, injection and signs of inflammation. I then do a tear-film breakup time with fluorescein. Anything less than 10 seconds on the tear-film breakup time test is abnormal. Then, I push on the lids to assess the meibomian glands and do the osmolarity, MMP-9 and meibography. If any of those tests are positive, we initiate treatment," Dr. Mah adds.

Part 3 of the algorithm is treatment, which is based on the subtypes and severity of ocular surface disease.

According to Dr. Mah, treatment can include topical steroids, such as loteprednol or fluorometholone, or an FDA-approved dry-eye medication like cyclosporine or lifitegrast. "The algorithm recommends being very aggressive for cataract and refractive surgery patients because they don't want to wait weeks or months for surgery," he avers. "Surgeons also don't want to wait. They want to optimize the surface, optimize their biometry, optimize their topography, optimize their preoperative measurements, and then get going with surgery.

"This is a little bit different than how we normally treat dry eye," Dr. Mah continues. "Typically, we start off with education, lifestyle changes like taking breaks from computers, and using over-the-counter artificial tears. Then, you kind of ramp up to other therapeutic modalities like using lifitegrast or cyclosporine, or managing the evaporative component by doing lid scrubs or warm compresses or some of these other in-office or even at-home treatments, like BlephEx, NuLids (NuSight), TearCare (Sight Sciences) or LipiFlow (Johnson & Johnson). Before cataract or refractive surgery, you

want to be a little bit more aggressive, try to quiet the eyes, and get the eyes normal faster so that you can get repeat measurements and do your surgery, hopefully within two to four weeks."

According to Rajesh Rajpal, MD, who is in practice in McLean, Virginia, and is the recently appointed chief medical officer for Johnson & Johnson Vision, treating surgical patients often requires a combination of dry-eye treatments. "We would consider artificial tears, meibomian gland treatment—whether it's warm compresses or a thermal device—and anti-inflammatory medications, as well as evaluating for potential environmental modifications," he says. "We also consider any contributing medical conditions, as well as any medications that the patient may be taking that can cause a drying effect. It is also critical after initiating appropriate treatment that when we're measuring for the IOL, we pay attention to the readings. If the ocular surface isn't ready, then we would either not do the readings or we'd repeat the readings to confirm the surface's stability before proceeding with surgery," he says.

Dr. Rajpal adds that it's often necessary to use a mild steroid in these patients because it frequently allows the surface to improve more quickly, as most patients want to have surgery relatively soon. He emphasizes the importance of detecting and treating dry eye that's present preoperatively so that the patient doesn't think it was caused by the procedure. "Postoperative treatment regimens are generally similar to preoperative treatments. We also want to make sure that the perioperative medications, such as antibiotic or nonsteroidal anti-inflammatory medications aren't causing some irritating or toxic effect," he cautions.

According to Dr. Mah, following this algorithm will produce better results in dry-eye patients. "That's been shown; you're definitely going to get better results by, number one, thinking about ocular surface disease; number two, diagnosing ocular surface disease; and then number three, treating ocular surface disease prior to doing any surgery," he says. "I think it has to be a mindset that you go into examining these people and trying to identify these patients prior to any of your measurements, and definitely before the surgery. You'll get better results."

Postoperative Outcomes

To achieve the best postoperative outcome, the key is to manage ocular surface disease preoperatively and carry management through the perioperative period, says Dr. Sheppard. "Prior to measurements, we give them preservative-free tears, a topical anti-inflammatory like cyclosporine or lifitegrast, or a steroid, specifically loteprednol," he says. "We put them on some type of lid hygiene, we give them oral essential fatty acids, we place a punctal plug, and we often go to the second tier of therapy with thermal pulsation or other means of rapidly improving their lid component. Once the surface is clear, the measurements are taken and the surgery is performed, we maintain the patient on that same preoperative regimen because a corneal or lens-based refractive procedure places a great deal of stress on the ocular surface. It anatomically damages—hopefully temporarily—the corneal nociceptor nerve complex, and the addition of perhaps stronger and preserved medicines can also temporarily stress the ocular surface.

"This concept is particularly true for the cataract patient, especially if one is performing a limbal relaxing incision, because the primary and secondary incisions sever corneal nerves, and limbal relaxing incisions sever even more corneal nerves," Dr. Sheppard continues. "That's one motivation for me to recommend a toric intraocular lens instead of a limbal relaxing incision. We now have a 0.75-D toric lens from Bausch and Lomb, so we can treat the patient's astigmatism in almost all circumstances with an intraocular lens that does not in any additional way disturb the ocular surface. The stress of cataract surgery, of course, also involves a bright light in the eye, a speculum holding the eye open, excessive drying and extra medicines—such as steroids, nonsteroidal anti-inflammatory drops, and antibiotics—that can damage the ocular surface, as well."

Dr. Sheppard explains that the management strategies for dry eye move along a continuum. "Pre-, intra- and postoperative measures are very important," he says. "In some severe cases, we immediately resort to higher-order therapies. Some practices use intense pulsed light, Maskin probes [Rhein Medical], TearCare or BlephEx. We use thermal pulsation. We often use an amniotic membrane to 'quick tune' the ocular surface. Severe cases may need more drops, more plugs, additional surface procedures and more visits. The ultimate goal is to normalize topography and obtain an outstandingly consistent manifest refraction." REVIEW

Dr. Mah has a financial interest in Allergan, Novartis, Sun, TearLab, Kala Pharmaceuticals, J&J Vision, NuSight and SightSciences. Dr. Sheppard has a financial interest in Alcon/Novartis, Kala, Lacriscience, Novaliq, Noveome, Ocular Therapeutix, Shire and TearLab.

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Is There Still Room for PK?

Christine Leonard, Associate Editor

Experts discuss PK's challenges and times when it's still the preferred procedure.

For years, penetrating keratoplasty was the go-to procedure for corneal transplants. Then came disease-focused transplant techniques—endothelial and lamellar keratoplasty—that supplanted the "one-size-fits-all" approach of traditional PK with increasingly refined surgical options, tailored to specific indications. The number of endothelial transplants surpassed full-thickness transplants around 2012.[1] Since then, penetrating keratoplasty has seen a slower increase in surgery volume, compared to EK.[1-4,8,9] But this trend doesn't mean that penetrating keratoplasty is going away; PK just has fewer indications than before. Here, experts discuss the shifting landscape of keratoplasty procedures, concerns with full-thickness transplants and when a full-thickness penetrating keratoplasty is still warranted.

The Changing Landscape

The Eye Bank Association of America reported for 2019 that the number of penetrating keratoplasty grafts increased by 0.4 percent (to 17,409 grafts) and endothelial keratoplasty increased by 1 percent (to 30,650 grafts), largely due to a 23-percent increase in DMEK procedures.[1] "That's almost double the volume of penetrating keratoplasty," says Thomas John, MD, clinical associate professor at Loyola University Chicago and in private practice in Oak Brook, Tinley Park and Oak Lawn, Illinois. "What's happened over time is that we had one choice—PK—and now we have much more advanced, selective corneal transplant options for lamellar or endothelial keratoplasty."

"Just 15 years ago, keratoplasty was almost exclusively penetrating keratoplasty," says Kenneth R. Kenyon, MD, clinical professor of ophthalmology at Tufts University School of Medicine/New England Eye Center and faculty member at Harvard Medical School and the Schepens Eye Research Institute. "Then came the revolution, as both anterior and posterior lamellar techniques were devised to manage tissue-specific corneal issues. Now in the United States, endothelial keratoplasties—DSAEK or DMEK—comprise at least 50 percent of the keratoplasties.

"Anterior lamellar keratoplasty for corneas with healthy, functional endothelium, also has an increasing role, particularly for keratoconus and stromal scarring from trauma and microbial keratitis," Dr. Kenyon continues. "Especially in the devel-

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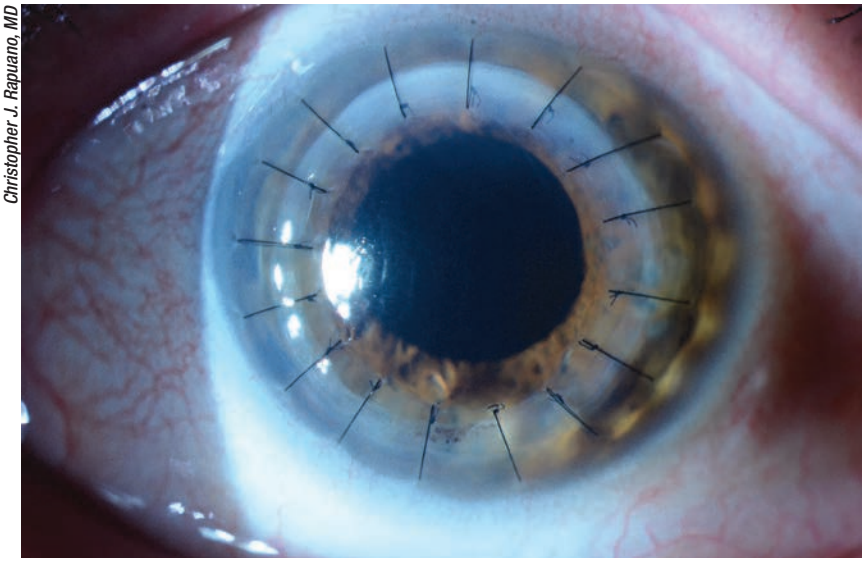
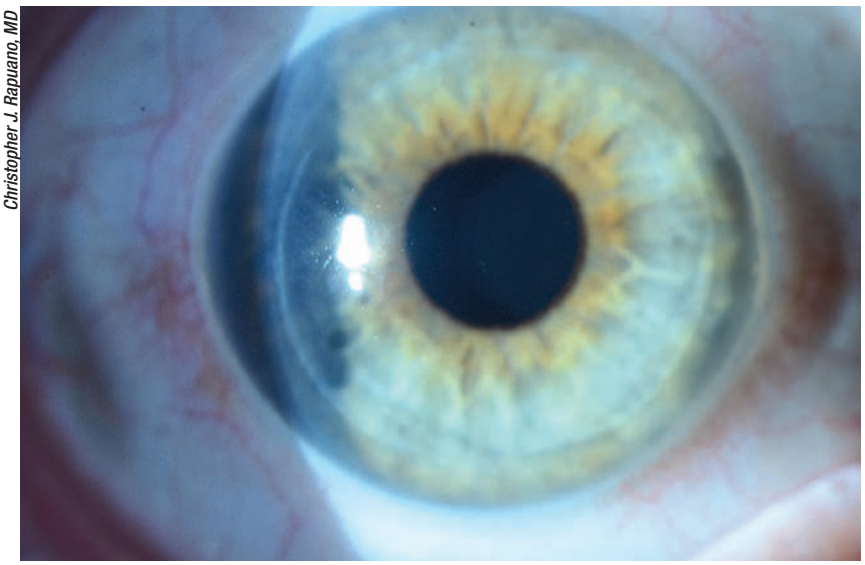
Christopher J. Rapuano, MD



A clear PK in a patient with a history of hydrops from keratoconus. Monitoring the sutures during postop healing is important. If sutures become loose and stay in the eye for days or weeks, infection can ensue or graft rejection may be induced, surgeons say.

Christopher J. Rapuano, MD



A clear DSEK in a patient with a history of Fuchs' dystrophy who developed corneal edema after cataract surgery. As a less invasive, endothelial procedure, DSEK carries less risk of rejection and heals faster than PK, according to corneal specialists.

oping world where these conditions are most prevalent and where corneal donor tissue remains undersupplied, ALK is advantageous, since it's rejection-free and doesn't require the highest quality of corneal donor tissue material. In such circumstances, perhaps 25 percent of transplants utilize ALK techniques."

Christopher J. Rapuano, MD, at Wills Eye Hospital in Philadelphia, adds that anterior lamellar grafts existed alongside penetrating grafts for decades, "but they were used at a very low level for a long time, because the techniques and results weren't very good. When the big bubble technique came out, we started doing more DALKs, which is a better procedure than PK—the main advantage being that there's no endothelial rejection. Having said that, it's a tricky procedure and many believe the visual results aren't as good as PK."

PK comprises perhaps 30 percent of cases, according to Dr. Kenyon. "These cases have either a combination of stromal scarring, thinning, ulceration or distortion that's not amenable to DALK and is often accompanied by endothelial failure, which requires more than a DSAEK. For such patients, penetrating keratoplasty remains the appropriate strategy."

Sometimes Less is More

While penetrating keratoplasty still has a role to play in the surgeon's toolkit, there are several reasons why it's used less often today. Newer methods of corneal transplantation aim to maximize visual outcomes and recovery while using less tissue and achieving lower rejection rates.

Generally speaking, surgeons say that the less manipulation of the eye, the better. Dr. John says that unlike lamellar or EK procedures, secondary glaucoma can be an issue with penetrating keratoplasty. In terms of graft rejection, "it appears that the amount of new tissue put in is directly related to the amount of rejection," says Dr. Rapuano. "A big, full-thickness graft has a much higher chance of rejection than a smaller DSAEK or DMEK graft." With anterior lamellar grafts, rejection is nearly nonexistent.

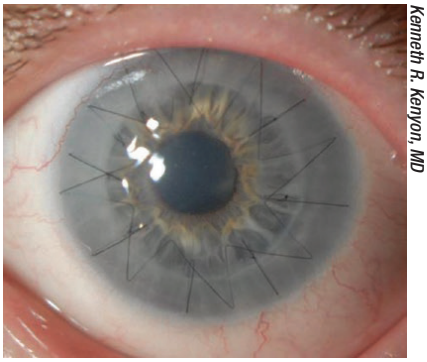
Here are some of the drawbacks to PK that encouraged innovation in less-invasive methods:

• ***Risk of rejection.*** "Less immune graft rejection is perhaps the most compelling advantage of not doing PK," says Dr. Kenyon. "Long-term studies of DSAEK and DMEK

procedures have clearly proven superiority in this respect. The PK failure rate due to rejection might be around 10 to 15 percent within a decade, depending on diagnosis and case-specific risk factors, since grafts for uncomplicated corneal edema or keratoconus enjoy high success rates, whereas a chemical burn with stem cell deficiencies or herpes keratitis with recurrence risks have higher risks for graft failure. The prognostic spectrum is very broad and often multifactorial.

"Painting with such broad strokes, let's suggest that the PK failure rate from rejection might be 15 percent within 10 years, whereas DSAEK reduces that risk to about 5 percent," he continues. "The real game-changer is the DMEK procedure, which reduces the rejection risk to about 1 percent—again, recognizing that DMEK is typically performed in the most favorable prognostic groups such as endothelial dystrophy or dysfunction, absent other risk factors. Nonetheless, such low rejection rates are stunningly advantageous."

• ***It's an open-sky procedure.*** Though expulsive hemorrhage is rare, experts say it's still an operative risk. "Whenever you do PK, one thing to keep in mind is that unlike lamellar procedures, which are usually closed procedures, PK is an open-sky procedure," explains Dr. John. "Hence, with PK, there's always the risk of potential intraocular expulsive hemorrhage. In those cases, if the surgeon doesn't act fast enough, you can lose the intraocular contents on the table. To avoid this potential, devastating complication, it's important to minimize the time period between taking the patient's cornea off and grafting the donor tissue. If you're performing the procedure while your patient is under general anesthesia, ensure your patient is paralyzed. Expeditiously place the first four to eight interrupted sutures so that the corneal opening in the patient's eye is closed. If, during the procedure, for whatever reason, there's a sudden increase in the intraocular pressure, you can avert a possible expulsive hemorrhage and thus prevent the intraocular contents from coming out. Quick surgical action is required under pressure. Place the donor tissue and quickly suture at least the first four, but optimally, the first eight sutures. Sometimes the situation may even demand placing your thumb on the corneal opening to temporarily occlude it."



Kenneth R. Kenyon, MD

A postoperative image of DALK in a young patient with Hurler syndrome. DALK improves stromal clarity while avoiding many of the risks associated with PK.

"The patients who are at the highest risk for expulsive hemorrhage tend to be older or those with glaucoma, cardiovascular disease, potential bleeding issues or hypertension," adds Dr. Rapuano. "In cases like these, you might consider a full-thickness transplant too dangerous. Though they may not be perfect EK candidates, you could try an endothelial graft and improve the vision a good amount, but it might not end up being 20/20, as it could have been with a PK."

• ***Induced astigmatism.*** When it comes to visual outcomes, PK takes a backseat to EK. In endothelial procedures, the stroma remains unchanged; surgically induced astigmatism isn't as much of an issue as it is with PK. "Even with intraoperative keratometry and refractometry, induced astigmatism remains a major challenge for PK," says Dr. Kenyon, who refers to the process of selective suture removal and/or adjustment as "suture roulette." He says, "Despite attempting to place sutures of even tension and distribution, the corneal curvature is still distorted, and so-called 'sutures out' astigmatism may require a year or more to stabilize. In contrast, slipping in the 'little gift that keeps on giving' of healthy endothelial cells, à la DSAEK or DMEK, only minimally alters the refractive status of the eye. Hence, both the rapidity of visual recovery and minimal refractive shifts are major advantages for endothelial keratoplasty."

Intraocular keratoscopy can help a surgeon to qualitatively visualize the corneal astigmatism and take steps during surgery to decrease it. "Intraoperative suture techniques are used to help distribute the tension appropriately for the running sutures, and also to add or remove interrupted sutures to decrease the surgically induced corneal astigmatism," says Dr. John.

Dr. Rapuano notes that vigilant suture follow-up is also vital for postop healing. "Full-thickness transplants have a lot of sutures, so you want to make sure you follow those sutures," he says. "If they become loose, take them out quickly. Patients need to be told that if they have foreign body sensation or scratchiness or feel like there's something in the eye, they have to come in right away. If a loose suture stays in for days or weeks it can cause infection or induce rejection. The office staff also needs to be informed that if a patient who had a transplant calls with these concerns, he or she needs to be seen right away."

• ***Slow healing.*** Corneal incisions are very slow to heal, Dr. Kenyon points out. "The wound strength of

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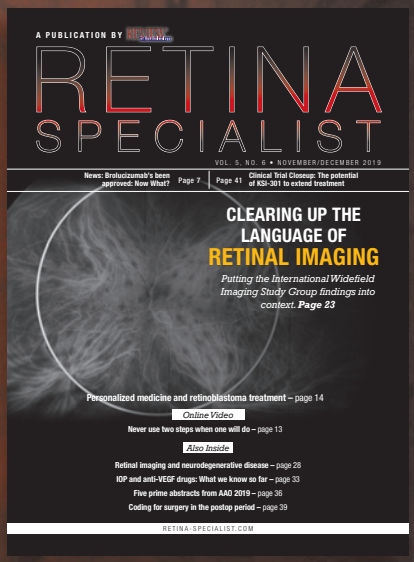

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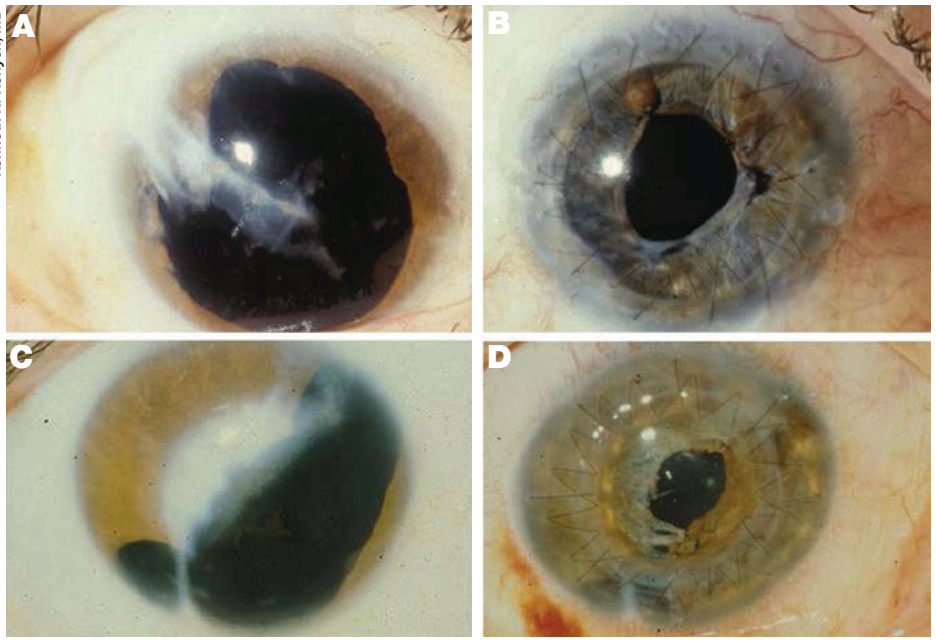


Kenneth R. Kenyon, MD

Four anterior segment reconstruction cases: (A) A monocular auto accident survivor underwent anterior segment reconstruction for corneal scar, extensive iris rupture and aphakia. (B) Iris remnants were used to recreate a central pupil along with PK and a posterior chamber IOL. (C) Patient had severe corneal and iris laceration but no lens injury. (D) Patient underwent PK with vitreous decompression to deepen the AC. An iris remnant was released and sutured to restore the central pupil while retaining a clear lens.

a corneal incision—and particularly of a full-thickness PK incision—isn't great," he says. "The wounds don't heal rapidly for two reasons. First, the cornea doesn't have any blood vessels, so the wound-healing process isn't promoted by neovascularization. Secondly, we're chronically using topical corticosteroids to reduce inflammation to prevent and/or treat rejection, which also inhibits stromal wound healing. As such, suture breakage or removal even years after PK can result in a major astigmatic surprise."

"With lamellar grafts, especially posterior lamellar grafts, the wound is stronger, and it's rare to have damage like a traumatic dehiscence," says Dr. Rapuano. "Endothelial grafts are the strongest. But with a full-thickness transplant, the eye is weak forever. The wound can break if you're poked in the eye, and if you're poked hard enough, the inside of the eye can fly out, resulting in blindness. We see PK dehiscences a couple times a week at Wills. Patients may fall or get hit in the eye and that'll open their transplant from 10 or 20 years ago."

"Given reduced stromal tensile strength, PK eyes are always more vulnerable to damage even consequent to relatively minor mechanical trauma," agrees Dr. Kenyon. "This can range from the non-vision-threatening, where a minor wound dehiscence requires additional suture replacement, to the catastrophic, where extrusion of iris and lens/IOL with potential expulsive choroidal hemorrhage can be irreversibly blinding. These are low-probability events, but they're high-risk in terms of severity of consequences."

Postop Complications

Ocular surface disease, induced astigmatism and graft rejection rank among the top causes of problems after full-thickness transplants. "Other complications are specific to the reason for the transplant in first place," Dr. Rapuano explains. "If you're doing a PK for a perforated ulcer due to infection, you have to worry about infection after the surgery. If you're doing it for herpes simplex, you'll be looking for a scar, and the patient may have inflammation. You'll also worry about healing, since the nerves are severely damaged in eyes after herpes simplex or herpes zoster. A recurrence of herpes, especially herpes simplex, after a transplant is another concern."

Who Still Needs PK?

"When the problem is throughout the entire cornea, that's where a full thickness graft would be most useful," Dr. Rapuano says. Here's a closer look at some major situations in which PK is still necessary:

• ***Both the stroma and the endothelium have severe damage.*** Corneal melts, perforated corneas, stromal scarring, corneal edema[5] and stromal thinning in the presence of endothelial cell dysfunction usually indicate PK. Additionally, Dr. John says, "infected corneal ulcers that don't respond to intensive antibiotic treatment, where the infection expands toward the limbus, will often need PK as a therapeutic approach (therapeutic penetrating keratoplasty, TPK) to save the globe."

In severe cases, such as in eyes with extensive infectious sclero-keratitis or corneoscleral destructive inflammatory or autoimmune disorders, extremely large-diameter corneal transplants (10 to 14 mm), sometimes including limbus and sclera, are man-

datory to save the globe, says Dr. Kenyon. He adds, "I call these 'commando' procedures because they serve as 'Hail Mary' efforts in a desperate effort to save the eye in hopes of returning subsequently for conventional PK plus whatever additional adjunctive anterior segment reconstructive efforts are required for visual rehabilitation."

• ***Trauma to the eye.*** "If there's been a laceration of the cornea, and it was repaired and healed up, you're often left with a full thickness scar in the cornea," notes Dr. Rapuano. "That's a full thickness problem, and typically a penetrating graft would work the best."

Your ability to restore the tissue may dictate your choice of transplant procedure, surgeons say. "For primary trauma, PK, although not often indicated, must be performed if major corneal tissue loss or ulceration doesn't allow anatomical restoration with conventional suturing and adhesives," says Dr. Kenyon. "Moreover, it's imperative to deal simultaneously with all other aspects of anterior segment damage such as iris tears or dialysis, irido-corneal synechiae, lens rupture or subluxation/dislocation, intraocular foreign body removal and/or vitreous prolapse or hemorrhage.[6] The 'open sky' approach, in concert with keratoplasty, at the very least facilitates access and exposure to the entirety of the anterior segment.

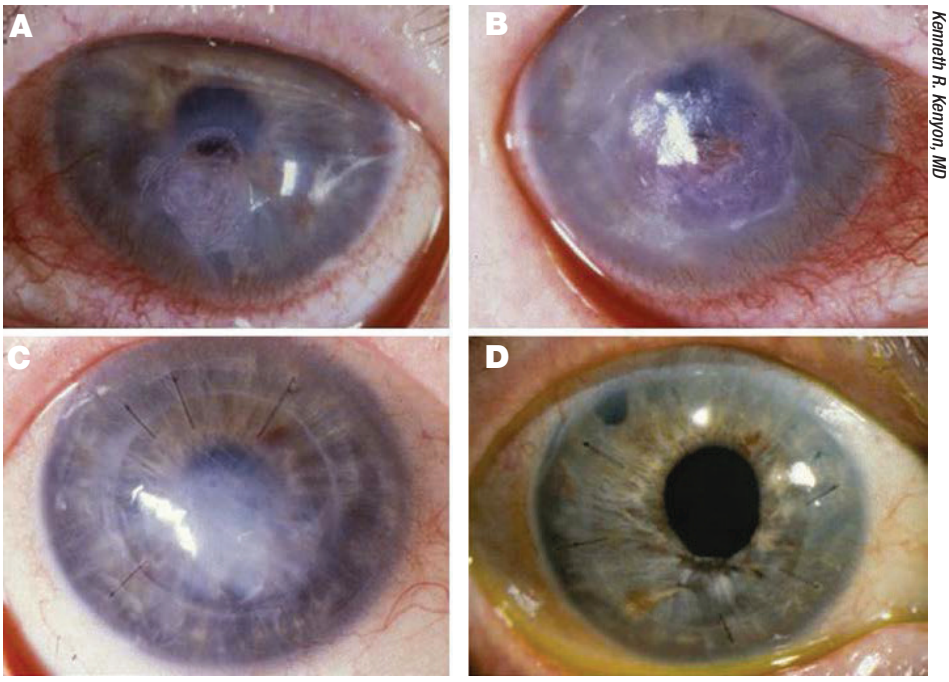
"Most post-trauma procedures that require complex reconstruction are performed months or even years after the original trauma," he continues. "Then you're working with an anatomically stable eye that's uninflamed and infection-free, may have undergone ocular surface restoration for limbal stem cell deficiency, has its intraocular pressure under control and is appropriate for a scleral- or iris-fixated IOL. I term corneal transplantation in these challenging scenarios 'PK Plus,' as the multiple aspects of anterior segment reconstruction are more readily achieved with the corneal 'lid' off than when completing the procedure with the almost incidental aspect of replacing a new cornea. Such concerted efforts are usually without additional complication risk. To the contrary, they're most often of visual, anatomical and cosmetic benefit."[7]

• ***Multiple, prior glaucoma or cataract surgeries.*** "This subgroup includes eyes that have had multiple surgeries for glaucoma and cataract with tube shunts and filters, extensive peripheral synechiae that need to be lysed or pupils that need to be reconstructed," says Dr. Kenyon. "These eyes are also traumatized by virtue of having undergone so many prior procedures. Although some cases that only involve corneal edema remain amenable to DSAEK/DMEK, for situations where we must also reposition or replace a tube shunt, lyse extensive iridocorneal synechiae, reconstruct a pupil and/or replace

an IOL, the open-sky strategy of PK remains most definitively applicable."

• ***Multiple, prior keratoplasty or keratorefractive surgeries.*** Dr. John says that "patients with failed DALK or DMEK transplants may also be potential candidates for PK, so as to avoid doing the same procedure over again. For those keratoconus patients with extreme corneal thinning, DALK may not be safe, and PK may be a better choice."

Dr. Kenyon adds, "These cases largely comprise a miscellany of situations involving prior penetrating keratoplasties, typically for keratoconus or pellucid marginal degeneration, which over many years have had progression outside the limits of the prior transplant and thereby present with resultant high astigmatism and/or ectasia that cannot be visually remedied, even with scleral contact lenses. Severe post-LASIK ectasia or, rarely, corneas that have had overly aggressive radial keratotomy surgery are also best remedied with PK, not only to restore corneal clarity but also to restore more normal corneal contour within the range of refractive correction possible with spectacles or contact lenses."



Kenneth R. Kenyon, MD

(A) A 72-year old woman with rheumatoid arthritis and keratoconjunctivitis sicca presents with a sterile stromal perforation that was initially stabilized with cyanoacrylate tissue adhesive. (B) A second tissue adhesive application is required to treat the progressive stromalysis. (C) To achieve tectonic stability, the patient underwent lamellar keratoplasty six months later, but her vision was still limited by stromal scars. (D) Another six months later, the patient underwent PK, synechiolysis, iridioplasty and extracapsular cataract extraction with a posterior chamber IOL. The patient achieved 20/50 visual rehabilitation.

PK is Here to Stay

"There still are definite indications for full-thickness transplants, though less so now than 25 years ago," says Dr. Rapuano. "The fellows at Wills get a lot of experience with full-thickness transplants. I think it's still important for training programs to train their fellows on full-thickness procedures."

Dr. John agrees. "In the corneal surgical arena, it appears that there will always be room for penetrating keratoplasty. When the visual axis is compromised by a full-thickness central corneal scar, it cannot be corrected by anything except a full-thickness penetrating keratoplasty. When PK is not a surgical option, in those subsets of patients, an artificial cornea such as the Boston Kpro may be considered."[10]

"In the span of just two decades, corneal transplantation has remarkably evolved and advanced from the PK-for-everybody era to the selective keratoplasty strategy for disease-focused management," Dr. Kenyon says. "Today, the tool box of the 'Compleat Keratoplaster' must necessarily contain the skillset from having mastered DALK and DSAEK/DMEK as well as having retained 'PK Plus' for the multiplicity of specific tissues and issues he or she encounters. Such creative choreography represents remarkable progress as well as promise for corneal transplantation in its many themes and variations." REVIEW

Drs. John, Kenyon and Rapuano report no relevant financial disclosures.

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A Sustained-release Glaucoma Treatment

Surgeons answer key questions about the newly approved option for keeping IOP low—without drops.

Christopher Kent, Senior Editor

The idea of a sustained-release implant that can deliver a drug slowly and steadily without requiring any patient action is certainly not new. However, making it a reality in ophthalmology has been challenging; creating safe and effective devices and getting them approved has taken years.

This March, doctors treating glaucoma finally got their first sustained-release option when the U.S. Food and Drug Administration approved Allergan's Durysta implant. The device contains 10 µg of bimatoprost, a prostaglandin analog, which is slowly released over a period of 12 weeks after it's injected into the anterior chamber. (Data from the clinical trials that led to approval suggest that its beneficial effects may last longer than that.) This implant may offer many patients a way to lower their intraocular pressure without having to use drops.

Here, doctors with experience using the implant during the clinical trials answer eight key questions about the new device and offer some thoughts about what may lie ahead for sustained-release treatments.

What Do the Studies Say?

E. Randy Craven, MD, an associate professor at Johns Hopkins University in Baltimore and former chief of glaucoma at King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia, participated in a multicenter Phase I/II, prospective, controlled, 24-month, dose-ranging, paired-eye clinical trial of the bimatoprost implant (the APOLLO study), involving 75 eyes of adult patients with open-angle glaucoma.[1] The study eye in each patient received an intracameral implant with either 6, 10, 15 or 20 µg of bimatoprost; the control eye received topical bimatoprost 0.03% drops. Rescue drops, or a single repeat administration of the implant, were permitted. The primary endpoint was IOP change from baseline.

Results included:

- At 24 months, mean IOP reduction from baseline was 7.5 mmHg for eyes with the 6-µg implant; 7.3 mmHg for eyes with the 10- and 15-µg implants; and 8.9 mmHg in eyes receiving the 20-µg implant. (IOP was reduced by 8.2 mmHg in the fellow eyes that received topical drops.)
- At six months, 68 percent of study eyes hadn't been rescued or retreated; at 12 months, 40 percent hadn't been rescued or retreated; and at 24 months, 28 percent hadn't been rescued or retreated.
- In terms of adverse events, those occurring in study eyes two days or less after the implantation were typically transient. After that point, the overall incidence was similar in study eyes and fellow eyes. However, the study eyes did show a lower incidence of some events typically associated with topical prostaglandin analogs. No incidences of endophthalmitis were encountered.
- If a second implantation was performed, the efficacy of the implant was similar to that of the first one.
- The implants gradually biodegraded after implantation. By 12 months, the majority of implants received at the first visit had either totally biodegraded or were estimated to be ≤25 percent of their original size.

The implant's efficacy was also compared to that of twice-daily topical timolol 0.5% drops in a pooled Phase III, 20-month-long, multicenter,

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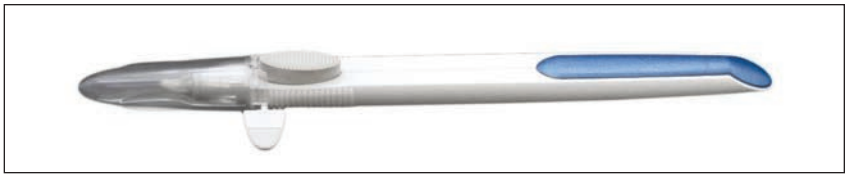

Above: The Durysta injector has an actuator button on the top side that's used to release the implant. (The tab sticking out on the underside of the injector is a safety mechanism that prevents unintentional implant release during shipping and handling.) Right: The implant is very small. It's designed to gradually biodegrade and eventually disappear after implantation inside the anterior chamber.

randomized, controlled clinical trial (ARTEMIS) involving 1,122 patients with open-angle glaucoma or ocular hypertension. In both groups, the implant reduced IOP about 30 percent from a baseline mean IOP of 24.5 mmHg (lowering IOP 5 to 8 mmHg) over the 12-week period.

The device was well-tolerated in the majority of patients; however, immediate post-injection irritation was noted, with 27 percent of patients experiencing conjunctival hyperemia, and 5 to 10 percent experiencing foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, irritation and increased IOP. Later, some patients experienced corneal endothelial cell loss, blurred vision, iritis and/or headache.

Felipe A. Medeiros, MD, PhD, Distinguished Professor of Ophthalmology, director of clinical research and vice chair for technology at Duke University in Durham, North Carolina, also participated in the trials of the new sustained-release device. He says that a preliminary post-hoc analysis of the ARTEMIS trials suggests that the implant may preserve the visual field better than timolol. "We found that over the course of one year, eyes randomized to Durysta had a slower rate of change in standard perimetry mean deviation than eyes that were randomized to timolol," he explains. "We're now retrieving more extensive data so we can look at this in more detail, with a longer follow-up time."

Who's Eligible?

Dr. Craven points out that the patient must have open angles to be eligible for the implant. "You need room to place it," he says. "Most primary open-angle glaucoma or exfoliative glaucoma patients would be good candidates. I probably wouldn't put one into an eye with corneal dystrophy or iritis.

"As far as safety, when two or three implants were in the eye the FDA was concerned that some of the patients had lower endothelial cell counts than at baseline," he continues. "However, I suspect the safety of the implant will improve as new versions are developed."

In terms of what might disqualify patients from receiving the implant, Dr. Medeiros agrees that patients with a history of angle closure or corneal diseases such as corneal dystrophy, or with a low endothelial cell count, wouldn't be eligible. "However, patients with these problems are relatively uncommon," he notes.

How Will It Be Used in Practice?

In terms of use in the clinic, Dr. Craven notes a number of considerations. "Clinics may find different ways to offer this option to patients," he says. "Some doctors may simply put it in whenever a patient requests it. Others, like me, may schedule a given day as an implant clinic and do multiple patients in a row. One reason for setting it up this way is that it's easier to make sure we have insurance approval, and that the specialty pharmacy has sent the implant for each patient. The other reason is that I'll most likely be using our minor procedure room to do this, and I've found that mobilizing the clinic team is easier if you do several patients in a row."

"Patient prep would be similar to that done for other intracameral or intraocular injections performed in the office," says Dr. Medeiros. "The procedure itself can be done at the slit lamp and should only take a few minutes.

Dr. Craven agrees. "We'll use topical anesthesia and topical Betadine," he explains. "The implant injector has a 28-gauge, sharp, fine needle. It takes a few minutes to do the whole procedure, and we avoid talking, and/or wear a mask, during the injection. The procedure can be done at the slit-lamp or in a minor room, or even in the OR if you want."

Dr. Medeiros notes that there are no clear guidelines regarding follow-up. "In general, I'd say patients could be seen one week later to make sure there are no adverse events," he says. "Some doctors might prefer to have a one-day evaluation as well. Long-term follow-up will depend on the individual patient, but in general, glaucoma patients are monitored every four to six months, and I'd expect a similar schedule with these patients."

"I'd probably follow up within a week and then every three to four months after that," says Dr. Craven. "Based on the Phase I trial data, I

think many patients will get more than six months of pressure control from the device. Some will get years of control."

What Do Patients Think?

Dr. Craven believes it's too early to draw conclusions about how patients will react to having the implant, but says he was seeing signs of interest in the clinic before the pandemic struck. "Some patients brought in Web clippings and asked about it," he recalls.

"During the study, most patients were in favor of going with the implant rather than drops," he continues. "About 80 percent of patients in the Phase I study reported being happy to not be using drops. This probably wasn't 100 percent because they still had to use drops in the non-implant eye.

"The implantation itself is minimally uncomfortable, with no pain, and no patients reported feeling it once it was in place," he adds. "None of the patients in the Phase I study requested removal. In the Phase III trial, a few were removed after several implants had been placed, but that was because the investigator was concerned about multiple implants irritating the cornea."

"Patients reacted very well to receiving the implant," agrees Dr. Medeiros. "The procedure isn't painful and they don't feel anything once the implant is in place; pretty much any discomfort reported was related to the Betadine used for sterilization during the procedure. Patients expressed great interest in being more free of drops with this treatment."

No More Adherence Issues?

"Lack of adherence with topical drops is a huge problem in glaucoma," notes Dr. Medeiros. "Data from multiple studies have shown that more than 50 percent of patients are poorly adherent, and this is associated with a worse visual prognosis. Also, many patients can't put in the drops because of coexisting disorders like rheumatoid arthritis. In many cases, family members or spouses have to put in the drops."

"It's important to understand that this treatment is not a free pass for patients to not come to see the ophthalmologist. Monitoring visual fields and optic nerves will still be essential."
— Felipe Medeiros, MD

Dr. Medeiros points out that while a sustained-release implant may address many problems associated with patient application of topical drops, there are caveats. "It's important to understand that this treatment is not a free pass to not come to see the ophthalmologist," he says. "Monitoring visual fields and optic nerves will still be an essential component of managing glaucoma in these patients.

"I don't think this will end the use of eye drops," he adds, "but having a long-term sustained implant opens up a lot of possibilities. By providing long-term IOP control, Durysta may help address adherence problems, and it may also help to improve the quality of IOP control, with fewer IOP peaks and fluctuations—although this remains to be demonstrated."

Helpful During the Pandemic?

In the current health crisis, Dr. Craven says the implant could be helpful for a patient forced into isolation in a nursing home. "A patient could achieve IOP reduction without the need for someone to put in drops," he notes. "We saw patients who were previously using one, two or three medications who did pretty well after receiving the implant and stopping the drops. I'll be presenting some of that data at this year's American Academy of Ophthalmology meeting."

What's Next?

As with any new treatment option, benefits and drawbacks that might not be revealed by a clinical trial will eventually become apparent in the clinic as doctors begin to use the implant. In the meantime, the current FDA approval only covers a single application of the implant, but other possibilities are under investigation.

"The Phase III clinical trials involved a total of three implants, with one application every four months," Dr. Medeiros points out. "Multiple studies are ongoing, or being planned, to address the safety and efficacy of multiple implants at different intervals of application. Hopefully, the results from these studies will support an FDA expansion of the current labeling."

In terms of what else may lie ahead, Dr. Craven says he believes this is only the beginning. "The technology and safety will continue to improve, and IOP control may improve as well," he says. "Other classes of medications may also be evaluated." REVIEW

Drs. Craven and Medeiros are consultants to Allergan.

1. Craven ER, Walters T, Christie WC, et al., for the Bimatoprost SR Study Group. 24 month Phase I/II clinical trial of bimatoprost sustained release implant (Bimatoprost SR) in glaucoma patients. Drugs 2020;80:2:167-179. doi: 10.1007/s40265-019-01248-0.

(Continued form page 26)

Mr. Hartley says he's published papers about using UV-C light sterilization, so he knows that it works against coronavirus. "My only concern is that you have to make sure the light is getting all the way through any folds or convolutions in the mask," he says. "With a soft, porous, fibrous surface, that can be tricky. Our colleagues in Nebraska have come up with a good process using UV-C light; they use two light devices instead of one, and they shine intense light on both the inside and outside of the masks. Hitting it from both sides with an excessive dose of light is probably the best way to use this strategy."

Mr. Hartley points out a helpful website that collates a lot of information about the sterilizing options. "Our protocol has been posted on the website N95decon.org," he says. "That's run by a not-for-profit consortium of medical professionals and academics who've looked at all the different ways people are trying to decontaminate PPE. They give a pretty nonbiased synopsis of all of the methods. They want to help people figure out how to accomplish this with whatever equipment they already have."

What's Next?

Given that constantly using and throwing away disposable, single-use items is arguably wasteful and harmful to the environment, it seems reasonable to wonder whether health care will return to that modality after the crisis ends. "If we can safely reprocess these one-time-use items, that's logical during this crisis," notes Mr. Hartley. "However, I suspect that when the crisis is over we'll probably go back to using disposable equipment.

"In the past, hospitals used surgical gowns that could be laundered," he recalls. "After each use they'd be laundered and sterilized and repackaged. The problem is, that's a fairly expensive process compared to using cheap disposal gowns. It's ironic that a large percentage of the disposable PPE is made in China and Asia where the outbreak started. It's a worst-case scenario. Having an outbreak like this will interfere with the supply chain of the inexpensive things that we rely on, and that could have a big impact on what happens after the crisis ends.

"So, I don't know if we'll return to the disposable system after this ends," he concludes. "Yes, cheap, disposable PPE is arguably wasteful. But if the cheap disposable stuff is back on the market and readily available, it may be too convenient to resist." REVIEW

Mr. Hartley and Dr. Cohenour have no financial ties or relationships with any technology discussed in this article. You can learn more about the SteraMist technology by visiting tomimist.com.

(Continued from page 36)

these technologies reliably for these patients by effectively screening them and following their disease course more easily than you could with fluorescein angiography, which is more invasive, more expensive, requires a lot of time and wears on patient tolerance. I think OCT angiography is quite compelling for the retinal specialist, who will be relying on OCT angiography a lot more than fluorescein angiography."

In the care of glaucoma patients, he continues, both perimeters and OCT units remain the mainstream technologies. "Updating to the use of newer, faster OCT machines will support the use of OCT angiography at some point, if not immediately," he points out. "I think that would be the time for glaucoma specialists to learn the uses of OCT angiography and, after acquiring the OCT angiography enhancement, start following their patients with this technology. In a few years, the analytics may provide an effective way to follow the patient in terms of monitoring progression and treatment response. Right now, there's not much of a consensus on OCT angiography in glaucoma. But it's something that's easily available, in terms of equipping the OCT machine and providing the scanning patterns. When you do an OCTA scan, you also get a high quality, 3-D structural scan from the OCT, so you can kill two birds with one stone—both the thickness measurement and the perfusion measurement. Using the same machine, you obtain two sets of data that can be used to validate each other. So, overall, I would say this new technology will be more and more beneficial for the practitioner." REVIEW

Dr. Huang has research grants, patent arrangements and stock ownership interests involving OptoVue. Dr. Weinreb receives research support and instruments for use in his practice and research from Optovue, Zeiss and Heidelberg Engineering. Dr. Richter still uses an OCTA unit donated to her by Zeiss in 2016 but has no relevant financial relationships with any OCTA manufacturer. Dr. Van Tassel reports no relevant financial relationships.

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Adding Pre-Descemet's Layer to EK

Experts explain how to use the sturdy pre-Descemet's layer in endothelial keratoplasty procedures.

Priya Narang, MS, Ahmedabad, India, and Amar Agarwal, MS, FRCS FRCOphth
Chennai, India

In recent years we've seen a flurry of activity in the corneal transplant arena, from front (deep anterior lamellar keratoplasty) to back (starting with Descemet's stripping automated endothelial keratoplasty). All of these new methods have the goal of minimizing the tissue used, minimizing rejection and maximizing the speed and quality of visual recovery.

Pre-Descemet's endothelial keratoplasty[1] is a newer variant among the endothelial keratoplasty procedures, and it involves the use of Pre-Descemet's layer (PDL) or Dua's layer[2] in the endothelial keratoplasty procedure. Though the technique is new to many surgeons, it has the potential to yield very good outcomes and may offer several advantages over previous methods. Here, we'll explain how to get good results with PDEK.

New Layer, New Potential

In 2013, Professor Harminder Dua, MD, FRCS, chair and professor of ophthalmology at Queens Medical Centre in Nottingham, United Kingdom, and his research team demonstrated a novel pre-Descemet's layer in the human cornea.[2] Using the big bubble technique of deep anterior lamellar keratoplasty, the team injected air into the stroma of donor sclerocorneal discs and performed peeling of the Descemet's membrane both before and after the creation of the big bubble.

They found three distinct types of big bubble: type-1, a well-circumscribed, central, dome-shaped bubble up to 8.5 mm in diameter; type-2, a large, thin-walled big bubble that always began at the periphery and enlarged centrally to form a maximum 10.5-mm diameter big bubble; and a mixed third type.

In contrast to a type-2 bubble, Descemet's membrane could be peeled off completely without deflating the type-1 bubble. That meant there had to be an additional layer of tissue present. Furthermore, a type-1 bubble could be created after first peeling off Descemet's membrane, confirming for the team that Descemet's membrane wasn't essential to the creation of a type-1 bubble.

Histologic examination of the tissue confirmed that cleavage occurred beyond the last row of keratocytes. The new layer identified by the team measured 10.15 ±3.6 µm and was composed of five to eight lamellae of predominantly type-1 collagen bundles in transverse, longitudinal and oblique arrangements.

Dr. Dua's team suggested that this layer acts as a splint to the Descemet's endothelium graft, providing graft stability and preventing extra scrolling of the graft tissue.[1]

PDEK Steps

The PDEK process isn't too different from traditional endothelial keratoplasty procedures, but it does rely on creating a good type-1 bubble at the start. Here are the steps for a successful PDEK graft:

1. Donor graft harvesting. The PDEK procedure specifically depends on the formation of a type-1 bubble during donor graft preparation.[2] A type-1 bubble has a distinct edge and spreads from the center to the periphery.

First, the corneo-scleral rim is placed with the endothelial side up.

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A 30-gauge needle attached to a 5-ml air-filled syringe is introduced from the rim into the mid-periphery of the corneal stroma. Air is then injected, which leads to the formation of a type-1 bubble. The edge of the bubble is punctured with a side-port blade and trypan blue is injected inside the bubble to stain the graft. The graft is then cut all around and harvested (*Figure 1*).

2. Recipient bed preparation. The recipient bed preparation is essentially the same as in other EK procedures. In cases with long-standing edema, the epithelium is usually debrided to enhance intraocular visibility of the tissues. To prepare the recipient bed, a paracentesis is made, and air is injected inside the anterior chamber. Next, descemetorhexis is performed with a reverse Sinskey hook, and the diseased DM-endothelium-complex is stripped and removed.

3. Donor graft injection. To inject the harvested donor graft, the graft is loaded onto the cartridge of a foldable intraocular lens where the spring of the injector system has been removed.[3] The graft is then injected inside the anterior chamber. Using air and fluidics, the donor lenticule is unrolled. The surgeon must ensure that the graft is properly oriented before injecting air beneath the graft—this will ensure graft adherence to the recipient bed inside the anterior chamber.

Seal the corneal incision with a 10-0 suture. The anterior chamber should be filled completely with air to provide adequate tamponade to facilitate graft adherence (*Figure 2*).

4. Postoperative care and management. Immediate postoperative care mandates that the patient lie flat for at least an hour. We prescribe a topical combination of antibiotic and steroid, tapering the dose over a period of two months. At every follow-up, anterior segment OCT evaluation is used to assess the graft positioning.

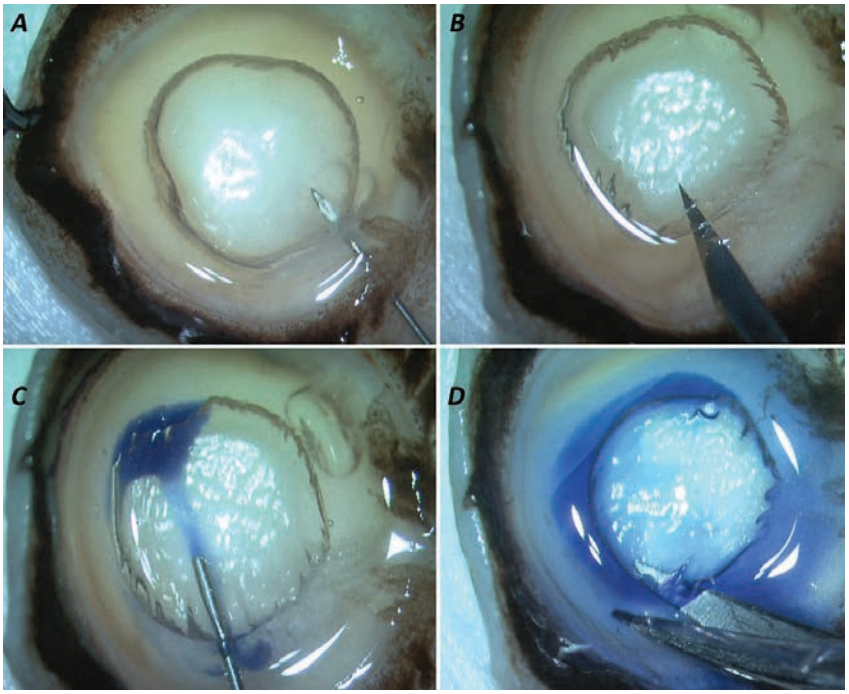

Figure 1. Donor graft harvesting. (A) An air-filled 30-ga. needle is introduced from the corneo-scleral rim up to the mid-periphery, and air is injected to create a type-1 big bubble. (B) The big bubble is punctured at the extreme periphery with the help of a side-port blade. (C) Trypan blue is injected to stain the big bubble. (D) The graft is cut along the peripheral edge of the big bubble with corneo-scleral scissors.

Techniques for PDEK

Now that we've gone over the steps for performing a PDEK, here are some techniques you may find useful to get the most out of the procedure:

• ***Endoilluminator-assisted PDEK.*** Patients undergoing EK procedures often have hazy corneas, which makes it difficult to assess the correct orientation of the donor lenticule. Proper graft orientation must be maintained. Under such circumstances, an endoilluminator can be used to project light obliquely onto the corneal surface. This provides transillumination that makes it easier to see the donor lenticule.[4] The PDEK lenticule rolls out with the endothelial side on the outer side of the roll, as seen in DMEK.

• ***Combined procedures.*** Cases of endothelial decompensation as a sequel to IOL subluxation and decentration often necessitate a combined procedure that can be performed in one or two stages; this clearly depends on the surgical scenario, as well as the surgeon's preference. Usually the IOL-fixation-based procedures involve either an IOL explantation or a refixation of the same IOL. Again, this depends on the surgical scenario, as well as the treatment procedure adopted for the case.

• ***PDEK with glued IOL.*** Here, the primary combination procedure involves IOL fixation/re-fixation with the glued IOL technique (*Figure 3*).[5,6] We prefer to perform a single-stage procedure. In this approach, begin with a glued IOL and follow this with a pupilloplasty procedure.

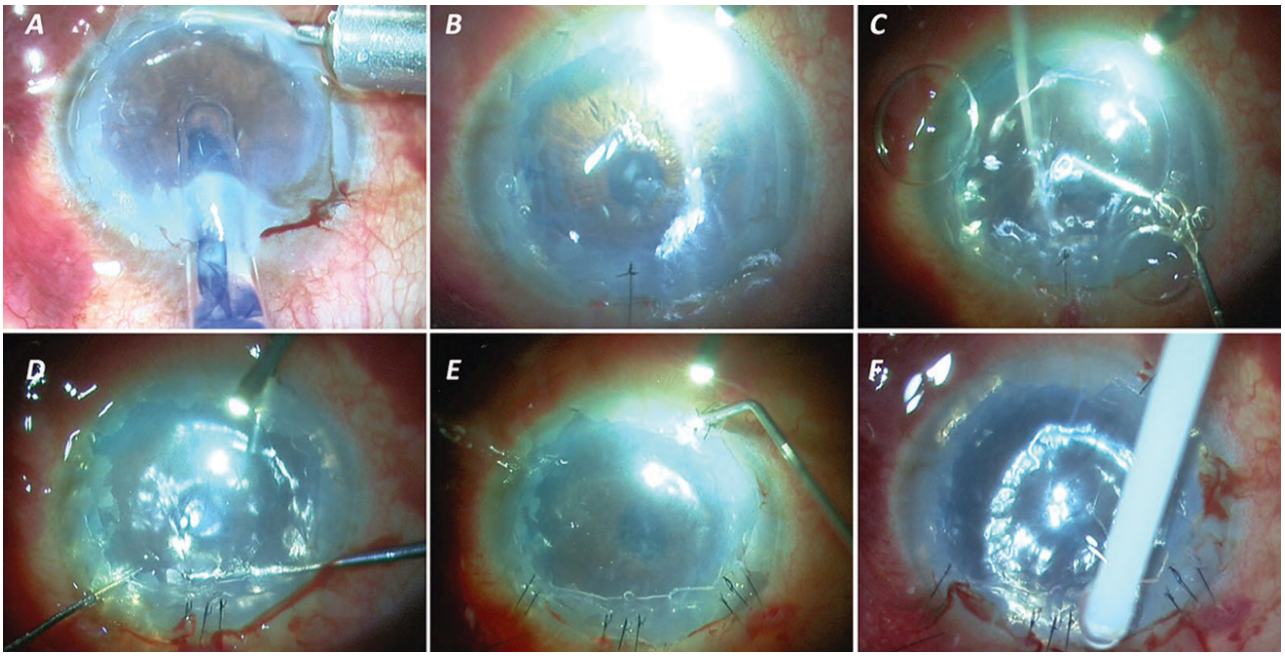

Figure 2. Donor graft insertion. (A) The donor graft is inserted into the anterior chamber. Wound-assisted graft insertion is avoided. (B) The donor graft lies within the anterior chamber. (C) Graft unrolling is attempted with air and fluidics. An endoilluminator is used to enhance graft visualization and also to check that orientation is correct. (D) The periphery of the unrolled graft is gently manipulated with a reverse Sinskey hook. (E) After proper centration and unrolling of the graft, air is injected beneath the graft, and all of the corneal wounds are sutured. (F) The tautness of the globe is confirmed.

Pupil reconstruction in these cases gives you several advantages. Often, the pupil is distorted due to vitreous prolapse; that eventually leads to endothelial decompensation. Pupilloplasty narrows the pupillary aperture and along with the IOL, acts as a barrier that helps to compartmentalize the eye efficiently into the anterior and posterior chambers. Pupilloplasty also prevents the escape of air into the vitreous cavity, facilitating the air tamponade and promoting graft adherence.

• ***Double-infusion cannula technique.*** The double infusion cannula technique (DICT) involves placing a double-infusion cannula inside the eye for a combined procedure of PDEK with glued IOL.[7] To facilitate the vitrectomy procedure and to prevent the collapse of the eye, we use posterior chamber fluid infusion. Air infusion in the anterior chamber makes up the second infusion to facilitate the PDEK procedure.

Vitrectomy associated with a secondary IOL implantation leads to decompression of the posterior chamber, but this is nullified by continuous fluid infusion inside the eye. Continuous fluid infusion in a PDEK procedure prevents tonicity of the eye. A continuous seepage of fluid inside the anterior chamber helps prevent the deepening of the chamber post-vitrectomy.

• ***PDEK clamp.*** Dr. Dua and his team designed a PDEK clamp that enables the appropriate handling of donor sclero-corneal discs for achieving a type-1 bubble with appropriate air injection into the corneal stroma. The clamp has a side port for the insertion of the needle, which can be attached to an air-filled syringe. The clamp has two 9-mm diameter rings that prevent air from escaping and that facilitate the formation of a type-1 bubble by closing the fenestrations in the periphery of the PDL, thus avoiding the formation of a type-2 bubble.

• ***Type-2 bubble trouble.*** Occasionally, a type-2 bubble is formed instead of a type-1 bubble. The clinical situation then requires DMEK to be performed instead of a PDEK procedure. Pre-cut PDEK tissue is currently available to help the surgeon overcome the uncertainty of graft preparation and potential monetary loss.

Where PDEK Fits in EK

The visual outcomes of UT-DSAEK and DMEK have been found to be comparable throughout the entire follow-up period, and better than DSAEK outcomes, in terms of final 20/20 visual acuity and speed of visual recovery.[9] This suggests that thicker donor tissue leads to greater interface haze and other refractive problems.

The spectral domain-OCT *in*

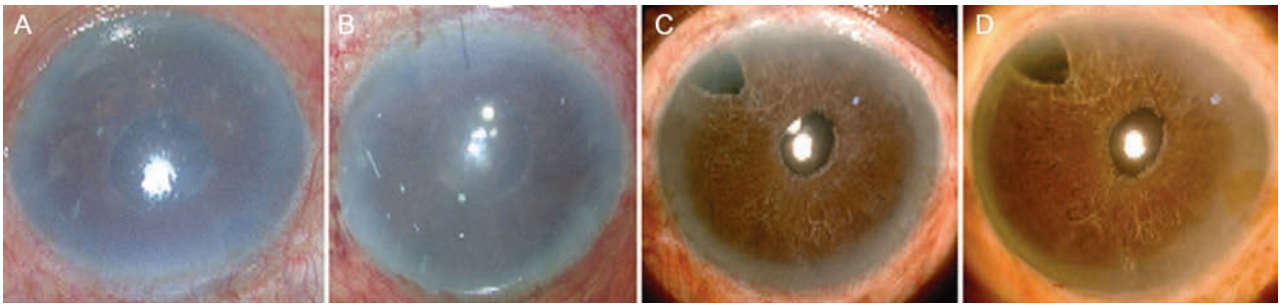

Figure 3. PDEK with glued IOL. (A) Preoperative image of a case with aphakia and endothelial decompensation. (B) One week after glued IOL. (C) Two months after PDEK. Vision 6/9 (Snellen equivalent 20/30). (D) Seven months after PDEK. Vision 6/6 (20/20).

vivo analysis of PDEK grafts has shown mean graft thickness at one-month follow-up to be 28 ±5.6 µm. This value is less than the thickness of donor tissue with UT-DSAEK (≤100 µm),[10] and is comparatively less than DMEK tissue.

Usually a donor age group older than 40 years is preferred for any EK procedure since it leads to less curling and rolling of the donor lenticule. In PDEK, peer studies have demonstrated the successful use of infant and young donor corneas too.[11] We surmise that this is due to the splinting effect of Pre-Descemet's layer on the lenticule, which eventually leads to less rolling/curling of the donor graft. PDL has been found to be sturdy enough to maintain a stable anterior chamber during cataract surgery in combined procedures with DALK.[12]

In summary, PDEK allows the employment of young donor tissue that's usually not possible with other variants of EK procedures. In addition, PDEK serves as an effective method to achieve good visual rehabilitation in patients with a compromised endothelium (*Figure 4*). REVIEW

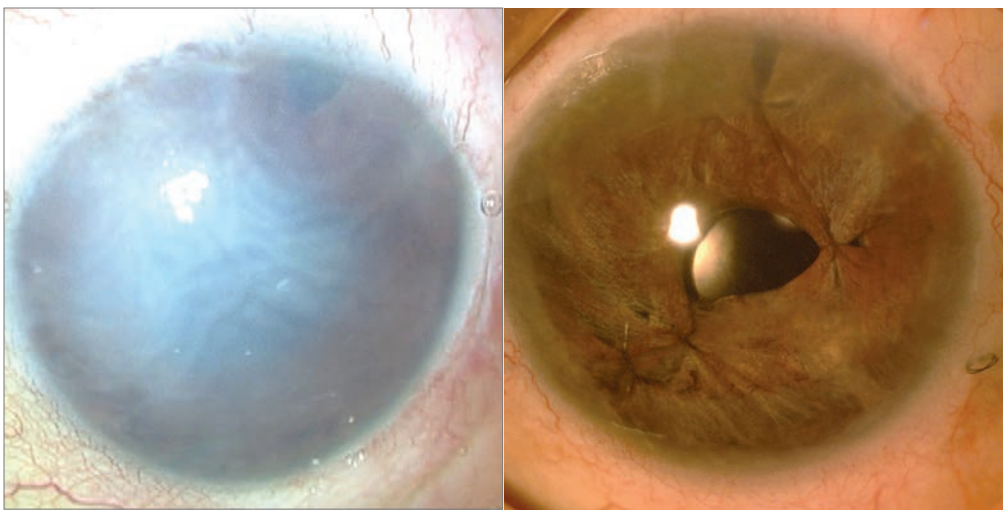

Figure 4. Preoperative (left) and postoperative (right) images of a PDEK patient.

Dr. Narang is the director of Narang Eye Care & Laser Centre, Ahmedabad, India. Dr. Agarwal is a professor and head of Dr. Agarwal's Eye Hospital and Eye Research Centre in Chennai, India. Neither has financial interest in any of the products mentioned.

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An Update on Surgical Viewing Systems

Surgeons delve into the pros and cons of a variety of vitreoretinal surgical viewing technologies.

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Adequate visualization is paramount to any successful vitreoretinal surgery. Although visualization may be impacted by various anatomic factors, the viewing system that the surgeon uses intraoperatively plays a significant role in achieving adequate visualization and, ultimately, successful surgical outcomes. The initial viewing systems that were used early in the development of pars plana vitrectomy provided a very limited angle of visualization. Today, however, we have a variety of viewing system options that provide excellent wide-angle visualization. This article will review these systems, which range from contact and non-contact wide-angle viewing systems to heads-up displays for 3-D vitrectomy.

Contact vs. Non-contact

Wide-angle viewing systems are routinely used in vitreoretinal surgery, and both contact and non-contact systems have benefits and limitations.

The popular Advanced Visual Instruments (AVI) contact system was developed in 1989; it consists of two lenses that provide excellent clarity for both macular pathology and the periphery, extending the field of view to 130 degrees *(Figure 1B and 1C)*[1] The clarity provided by contact systems is the result of their ability to compensate for corneal aberrations. However, scleral depression can be more challenging with a contact lens in place. These systems are associated with an increased rate of corneal abrasions, and a capable assistant is required to hold the lens in place.[2,3] Modified self-stabilizing lenses have been developed to reduce, but not completely eliminate, the need for a skilled assistant to hold the lens intraoperatively.[4,5]

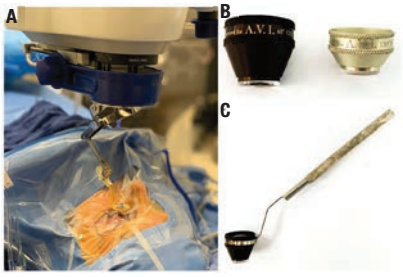

Figure 1. (A) Zeiss Resight non-contact wide angle viewing system. (B) Advanced Visual Instruments contact system consisting of 68-degree and 130-degree lenses. (C) AVI lens with handle for positioning intraoperatively.

Alternatively, non-contact systems eliminate the need for an assistant to hold the lens, but provide a slightly smaller viewing angle and reduced clarity in comparison to contact systems.[3] Previously, viewing system selection was based on surgeon training and preference, as there was minimal data available comparing anatomical and functional outcomes of contact versus non-contact viewing systems. In 2012, an abstract presented at the Association for Research in Vision and Ophthalmology compared outcomes of 33 eyes that underwent pars plana vitrectomy with either a non-contact viewing system (the Optical Fiber Free Intravitreal Surgery System, or OFFISS) or a contact lens system, for a variety of retinal pathologies including retinal detachment, macular hole, lens dislocation, epiretinal membrane, vitreous hemorrhage, intraocular foreign body removal and silicone oil removal.[6] Despite the small sample size, this report found no statistically significant difference in operative time, postoperative visual outcomes, postoperative complications such as hypotony, intraocular pressure elevation, choroidal detachment or hyphema. However, there was more vitreous hemorrhage

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reported in the non-contact group.[6]

We recently compared anatomical and visual outcomes of patients undergoing non-complex retinal detachment repair with either a contact or non-contact viewing system as part of the Primary Retinal Detachment Outcomes Study.[7] This multicenter, interventional, retrospective, comparative study is the largest comparative study of contact versus non-contact viewing systems published to date.[7] In this study, we analyzed 2,256 eyes, of which 1,893 were repaired using a non-contact system and 363 were repaired using a contact-based system.[7] We found no statistically significant difference in single surgery anatomic success at three months postoperatively, or at the final follow-up visit (with an average follow-up of 337 days for the non-contact group and 229 days for the contact group).[7] Postoperative visual acuity was better in the contact group (logMAR 0.345 [20/44 Snellen]) compared to the non-contact group (logMAR 0.475 [20/60 Snellen]).[7]

There were multiple factors that could explain the difference in final visual acuity: better preoperative visual acuity in the contact group (logMAR 0.998; Snellen equivalent 20/199 in the contact group versus logMAR 1.134; Snellen equivalent 20/272 in the non-contact group); surgeons using the contact system were highly experienced (84 percent of surgeons in the contact group had over 15 years of experience); and longer follow-up in the non-contact group, which may have resulted in the formation of more mature cataracts.[7] However, when controlling for confounding variables in a multivariate analysis, viewing system was no longer statistically significant.[7] Therefore, given the excellent outcomes of both viewing systems, we recommended surgeons continue to operate with their preferred system (contact or non-contact).

Non-contact Systems

As detailed in the sidebar on page 68, the development of the first non-contact viewing system—the BIOM—in 1987 provided an alternative to contact-based viewing systems and eliminated the need for an assistant to hold the lens in place intraoperatively.[8] Since the development of the BIOM, multiple other non-contact wide-angle viewing systems have been introduced (also mentioned in the sidebar).[8] In 2012, a report compared five different non-contact wide angle viewing systems: BIOM (Oculus); Merlin (Volk Optical); OFFISS (Topcon); Resight (Carl Zeiss Meditec); and the Peyman-Wessels-Landers semi-wide-angle viewing system (Ocular Instruments).[3]

Of the five systems evaluated, the OFFISS obtained the widest angle of view (95 degrees in fluid and 125 degrees in air).[3] The report found the Resight system to be the least affected by pupil size and to have the least amount of image distortion when viewing the peripheral retina *(Figure 1A)*. Also, the report concluded the Resight provided the clearest view of the posterior pole.

Heads-up 3-D Viewing

Heads-up 3D viewing systems were initially used in anterior segment surgery and later adapted for use in vitreoretinal surgery.[9] Systems include the Ngenuity (Alcon), the Sony HD Medical Display and the Zeiss Artevo 800. In the case of Ngenuity, the system usually consists of a large display (around 46-inch) placed 1.5 meters from the surgeon and doesn't require viewing through the microscope eyepieces *(Figures 2A and 2B)*.[9]

An initial report on a heads-up 3-D system in 2016 evaluated speed, resolution, ease of operation and ergonomics for 20 participants performing three different tasks using the system as well as a traditional microscope.[9] The participants found the heads-up viewing system to have better ergonomics than traditional vitrectomy viewing systems.[9] In addition, the majority of participants found the image to be sharper and believed tasks could be performed equally fast or faster than with traditional vitrectomy viewing systems *(Figure 2C)*. One limitation noted was decreased resolution compared to traditional viewing systems, but the participants compensated by increasing magnification. This initial report also assessed the outcomes of 43 cases of vitrectomy with ILM peeling for macular holes performed by one surgeon using the heads-up 3-D system. These cases had excellent anatomic outcomes, with a 97.7-percent closure rate and only one case requiring reoperation. An additional benefit reported was the ability to decrease light source intensity which, theoretically, could reduce the risk of phototoxicity.[9] The cost of acquiring the heads up 3D viewing system, however, may be a barrier to large-scale adoption. For example, the Ngenuity system produced by Alcon costs approxi-

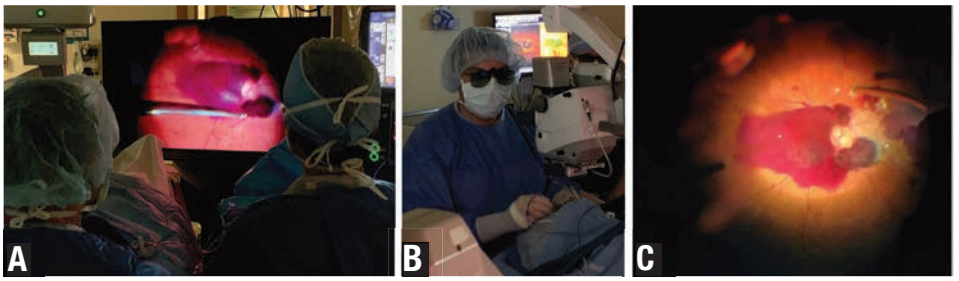

Figure 2. (A and B) Surgeon and display positioning while using the heads-up 3-D viewing system. (C) The view of the fundus with the heads-up 3-D viewing system.

A Brief History of Visualization in Vitreoretinal Surgery

Visualization in vitreoretinal surgery traces its roots to Japan in the early 1950s. At that time, techniques included direct visualization of vitreous via an open-sky technique, with later reports describing the use of closed vitrectomy.[1,2] These two techniques eventually became more popular following the reports of open-sky vitrectomy by David Kasner in the 1960s, and pars plana vitrectomy by Robert Machemer in the 1970s.[3,4]

In developing a closed pars plana approach, the need for improved visualization of the vitreous and fundus grew, which led to the development of an operating microscope with X-Y movement and a modified Goldmann fundus lens that provided a 20-degree view of the posterior pole.[5] This initial contact lens system used by Machemer, however, was complicated by frequent bubbles that obscured visualization. Therefore, this system was modified and connected to irrigation to eliminate the need for repeated replacement of viscous fluid.[6,7] The later development of biconcave contact lenses increased the field of view to 35 degrees.[8,9] The field of view was further increased with the development of prism contact lenses, which enabled visualization out to the equator in one quadrant at a time; however, this required rotating the lens to visualize the remaining quadrants. In addition, the view was compromised by distortion in the periphery and limited stereopsis.[7,10] These contact lenses were initially held in place by skilled assistants, but were later adapted to attach with low vacuum suction or sutured in place.[7] Nevertheless, sutured lenses were complicated by perilimbal hemorrhage and limited visualization of the extreme periphery.[7]

Wide-angle viewing systems arrived with the introduction of the pan-funduscope in 1969. Due to the creation of inverted imagery, their use was limited until the development of the stereoscopic diagonal inverter (SDI) in 1987.[11,12] The SDI reversed the inverted image and allowed for stereopsis, thereby enabling wide-angle viewing in vitreoretinal surgery; however, this visualization system didn't gain widespread adoption. Concurrently, the first non-contact viewing system, the binocular indirect ophthalmomicroscope, was developed by Spitznas and eliminated the need for a skilled assistant to hold the contact lens in place intraoperatively. The BIOM was widely adopted and represented a major breakthrough compared with the use of contact lens visualization systems. Since the development of the BIOM, additional non-contact systems have been introduced, including the Merlin, the Optical Fiber Free Intravitreal Surgery System (OFFISS), Resight *(Figure 1A)* and the Peyman-Wessels-Landers lens. Over time, the Resight has emerged as the most popular. The latest development in visualization in vitreoretinal surgery was the introduction of heads-up 3-D viewing systems *(Figure 2)* in 2016.

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mately $75,000. While there are likely no additional costs thereafter for continued use of the system, a practice must weigh whether this upfront cost justifies the additional benefits of the system versus operating with a traditional microscope. Another limitation noted in earlier 3-D viewing systems was an image delay however, this has decreased as the technology has improved.

More recently, a 2017 report compared traditional viewing systems versus heads-up 3-D displays for cases of retinal detachment.[10] These cases consisted of both primary, simple retinal detachments and complex, recurrent detachments. The report consisted of seven cases repaired with a 3-D system and 15 with a traditional viewing system. There was no statistically significant difference in terms of anatomic success at 30 days (p=0.74) and no major postoperative complications. There was no statistically significant difference in surgical time between the two groups (55 ±35 for the 3-D group and 62 ±28 for the control group, p=0.07). Mean endoillumination power was significantly lower in the 3-D group (10 percent versus 45 percent in the control group, p<0.0001). The researchers noted, however, that surgical time is influenced by the difficulty of each singular case, and that the homogeneity between approaches can't be guaranteed by a non-randomized retrospective comparison. Therefore, differences in operating time between the two systems should be "interpreted with caution."

A larger study of 326 eyes compared the outcomes of a traditional viewing system (Resight) versus a 3-D heads-up viewing system (Ngenuity) for cases of idiopathic epiretinal membrane, vitreous hemorrhage with and without tractional retinal detachment, macular hole, rhegmatogenous retinal detachment (primary and PVR-related), pathologic myopic foveoschisis, silicone oil removal and vitreous opacities.[11] This report found no statistically significant difference in postoperative visual acuity, anatomic outcomes or postoperative complications between the two groups.[11]

These reports didn't identify increased complications or significant differences in outcomes when comparing a heads-up 3-D viewing system to traditional microscope viewing systems for a wide range of surgical indications in vitreoretinal surgery. In addition,

the 3-D viewing systems may offer long-term ergonomic benefit.

In conclusion, since the development of pars plana vitrectomy in the 1970s, viewing systems have dramatically improved, resulting in excellent visualization in vitreoretinal surgery. Initial viewing systems, such as the modified Goldmann contact lens used by Machemer, provided limited visualization of the posterior pole, but subsequent innovations have increased the field of view and maintained excellent clarity. Non-contact wide-angle viewing systems have now become the standard in vitreoretinal surgery, allowing for excellent surgical results. In addition, the recent development of heads-up 3-D viewing systems can also lead to excellent vitreoretinal surgical outcomes and better ergonomics.

With each advance in viewing systems, visualization in vitreoretinal surgery continues to improve, and these advances ultimately lead to more precise surgeries and better patient outcomes. REVIEW

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Targeting Allergic Conjunctivitis

The pollen is out in full force, and Eyevance's Zerviate (cetirizine ophthalmic solution 0.24%) is here to help. Zerviate is the first novel prescription-only treatment for allergic conjunctivitis in 10 years, says Eyevance. The formula contains cetirizine, the same active ingredient found in the antihistamine Zyrtec. Additionally, the company notes that the drug's other ingredients—glycerin and hydroxypropl methylcellulose—commonly found in tear lubricants, comfortably facilitate the delivery of the cetirizine molecule to the eye. In the clinical trials, Zerviate demonstrated ocular itching relief within three minutes—and relief up to eight hours for moderate and severe allergic conjunctivitis—as well as relief of other ocular allergic conjunctivitis symptoms. Eyevance plans to launch virtual educational webinars to provide doctors with more information about Zerviate. Visit https://myzerviate.com/

New Releases from Icare USA

Icare USA's newest diagnostic instruments include the Centervue DRSplus—a confocal fundus imaging system—and the next generation of Icare USA's handheld tonometer line, the Icare ic200. Icare USA says the DRSplus uses white LED illumination to produce its 45-degree retinal images, which the company says are sharper, have greater contrast and better optical resolution (even through cataracts) than traditional fundus camera imaging. With the DRSplus' mosaic function, physicians can view panoramic 80-degree images. Icare says the DRSplus requires minimal training and will speed up exam time. The company says a physician with experience using the DRSplus can obtain high-quality color images for both eyes in less than 10 seconds.

The new ic200 handheld tonometer can test patients in different positions.

The Icare ic200 features a new streamlined design and user interface that confirms proper position for measurement through light indicators. Using a rebound measuring principle, the ic200 measures IOP without any anesthetic drops, air puffs or specialized skills, says the company. Additionally, Icare USA notes that this new model of handheld tonometer has the ability to test patients while they're sitting, supine or elevated. The company says the ic200 is accurate and reliable when compared to applanation, and its portability also allows the physician to acquire IOP information in eyes that are traditionally difficult to measure. Visit icare-usa.com.

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To help maintain six feet of social distance, Luneau Technology recently introduced a new digital phoropter, the Visionix VX65. The new device allows eye-care providers to control the entire refraction process using a tablet or an optional control panel, standing six feet away from the patient, or even in another room or office location, the company says.

Luneau says the VX65 makes integrating remote or digital refraction in the clinic easy with a familiar interface and the option to switch between manual and auto modes. The VX65 also allows users to export refraction data directly to their EHR and import data from external devices such as lensmeters.

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Wills Eye Resident Case Series
Edited by Rebecca Russ Soares, MD, MPH

A Boston Keratoprosthesis patient develops serious problems with her implant.

Matthew N. Pieters, MD, Kekul B. Shah, MD, Tatyana Milman, MD, and Sadeer B. Hannush, MD

Presentation

An 86-year-old Caucasian female with a Type 1 Boston Keratoprosthesis (KPro) in the right eye presented for routine postoperative follow-up with her cornea specialist 16 months after transplantation. During the first six months postoperatively, vision in the right eye remained 'hand motion' at worst to 'count fingers' at best, limited by glaucomatous optic nerve damage. However, the patient complained of persistent 'light perception' vision from postoperative month seven onward despite a laser membranectomy for a dense retroprosthetic membrane (RPM). No pain or increased redness was reported.

Medical History

Past ocular history included two failed traditional penetrating keratoplasties on the right eye in the setting of herpes zoster ophthalmicus, a neurotrophic ulcer and necrotizing herpetic stromal keratitis. Additional ocular history included primary open angle glaucoma, Fuchs' dystrophy, cataract extraction and lens implantation in both eyes and a Descemet's stripping endothelial keratoplasty on the left eye. Prior to the KPro implantation, the contralateral left eye had developed both early DSEK graft failure and visually significant scarring secondary to bacterial keratitis.

At the time of KPro implantation, visual acuities were 'light perception' in the right eye and 'count fingers' in the left eye. There was an initial small increase in visual acuity during the first six postoperative months as noted above. However, visual prognosis was limited by worsening glaucoma. By postoperative month seven, vision was only 'light perception' and no improvement was seen after a laser membranectomy. Throughout the postoperative period, the patient wore a soft contact lens and remained on topical ciprofloxacin, vancomycin and a steroid with good reported compliance.

Ocular medications at presentation: vancomycin 2.5% gtt b.i.d. OD; ciprofloxacin 0.3% gtt b.i.d. OD; prednisolone sodium phosphate 1% gtt b.i.d. OU; brimonidine 2%/timolol 0.5% gtt b.i.d. OU; ciprofloxacin 0.3% ointment qHS OS; bacitracin ointment qHS OS; acyclovir 400 mg b.i.d. by mouth.

Other past medical history was notable for breast cancer, hypercholesterolemia and a hiatal hernia. Systemic home meds included omeprazole, simvastatin and mirtazapine. Family and social history were noncontributory.

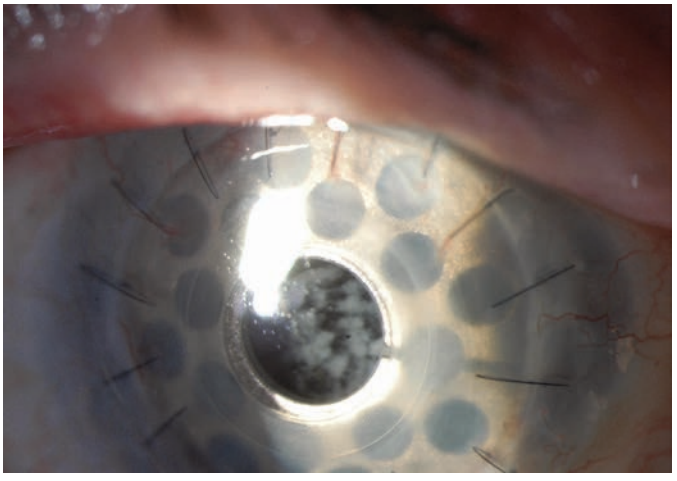

Figure 1. External photograph of the right eye demonstrating fluffy retroprosthetic opacities on the KPro.

Examination

Ocular examination demonstrated corrected visual acuities of 'light perception' OD and 20/200 OS with pinhole correction to 20/160. Confrontation visual fields were unable to be completed on the right and intact on the left. Intraocular pressure was estimated

at 10 mmHg tactile OD and 14 mmHg tactile OS. Motility was grossly full. Pupillary exam demonstrated a known, noted right-sided 2+ rAPD, thought to be due to glaucoma.

Anterior slit lamp examination of the right eye was most notable for several small white retroprosthetic opacities (*Figure 1*). The KPro/PK complex was in good position as was a soft contact lens. The rest of the exam on the right demonstrated mild conjunctival injection and two well-covered glaucoma drainage devices. Slit lamp exam also suggested the development of a fluffy vitreous opacity. Posterior exam on the right revealed 3+ optic nerve pallor with severe cupping and a grossly flat retina.

Anterior slit lamp exam on the left was notable for a 3+ superonasal corneal scar encroaching on the visual axis. The rest of the corneal exam revealed a well-positioned DSEK button and trace stromal edema. The conjunctiva was white and quiet, the AC was deep and quiet, iris was normal appearing and the PCIOL was well-centered. Posterior exam on the left revealed a 20/70 view to the posterior segment, mild optic nerve pallor with severe cupping and a grossly flat retina.

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

Workup, Diagnosis and Treatment

The differential for the new retroprosthetic opacities included recurrent RPM, but suspicion was strongest for a smoldering infectious process, including both bacterial and fungal etiologies, especially in view of the fluffy appearance of the retroprosthetic opacities and vitreous involvement. The patient was referred to her retina specialist who proceeded with a pars plana vitrectomy, vitreous biopsy and injection of intraocular antibiotics and antifungals (vancomycin, ceftazidime and amphotericin). A diagnosis of chronic fungal endophthalmitis was established when cultures grew *Candida parapsilosis*.

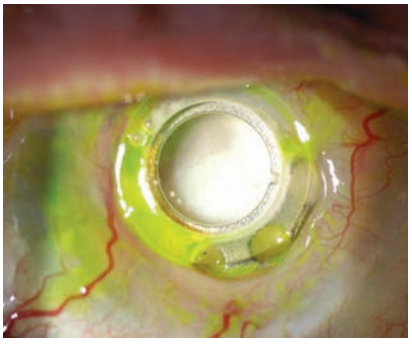

Figure 2. External photograph of the same eye two years later prior to enucleation demonstrating phthisical changes, peri-optic corneal melt in the carrier corneal graft (3 to 6 o'clock) and a dense white retroprosthetic opacity.

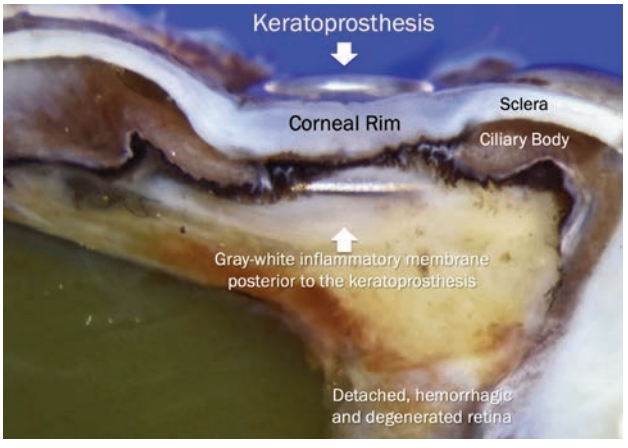

Figure 3. Gross pathology of the enucleated right eye demonstrating an inflammatory membrane adhering to the posterior aspect of the keratoprosthesis.

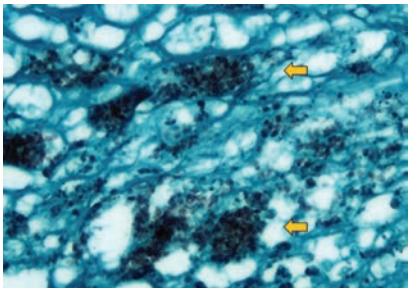

Figure 4: Giemsa silver stain from the enucleated eye demonstrating small yeast forms, consistent with *Candida parapsilosis*.

The patient was initially started on oral voriconazole by her retina physician and then switched to oral fluconazole. Despite these measures, the right eye developed peripheral proliferative vitreoretinopathy and a shallow peripheral retinal detachment on ultrasonography. Given the already limited visual potential, the patient opted for observation at that time. The retroprosthetic opacity continued to thicken and coalesce (*Figure 2*) and the eye eventually developed a funnel retinal detachment and progressed to phthisis over the next two years. The decision was made to enucleate the right eye. Pathology revealed a large grey-white inflammatory membrane behind the KPro (*Figure 3*) and Giemsa silver stain demonstrated small yeast forms compatible with *Candida parapsilosis* (*Figure 4*).

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Discussion

The Boston KPro is the most frequently used keratoprosthesis, or synthetic cornea, with over 15,000 units implanted.[1] This prosthesis consists of a back plate and optical stem that are incorporated with a donor cornea at the time of surgery. KPro implantation is primarily used when a standard PK is deemed unlikely to be successful, often after repeat PK failure.[2,3]

A 2015 review of the published literature on the safety and outcomes of Boston KPros found that development of a retroprosthetic membrane was the most common postoperative complication (30 percent), followed by glaucoma (27.5 percent).[4] Other anterior postoperative complications included corneal melt and infectious keratitis. Infectious endophthalmitis was the most common posterior segment complication (4.6 percent) across all studies, although rates appeared to be down trending.[4]

KPro-related endophthalmitis occurs as virulent organisms from the ocular surface gain access into the eye through an altered barrier layer along the course of the implant. In bacterial KPro-related endophthalmitis, these causative organisms are often gram-positive cocci including various staphylococcus and streptococcus species.[5] Prior to 1999, bacterial endophthalmitis was a formidable postoperative complication despite prophylactic antibiotic drops.[5] In 1999, the addition of prophylactic topical vancomycin drastically reduced the rate of endophthalmitis due to its excellent gram-positive coverage. One 2009 Massachusetts Eye and Ear study of 255 KPro eyes demonstrated that the addition of prophylactic vancomycin resulted in a 0.35-percent risk of endophthalmitis per patient-year, 12 times less than eyes that didn't receive vancomycin.[6] A 2009 Wills Eye study of 37 KPro eyes found four cases of endophthalmitis, three of which admitted to discontinuing vancomycin prior to infection, further demonstrating the importance of prophylactic adherence.[7]

A 2015 literature review of fungal infections—and both keratitis and endophthalmitis—after KPro implantation found that fungal infection rates ranged from 0.009 to 0.02 infections per patient-year, with the largest single-surgeon study reporting a 10 year fungal endophthalmitis incidence of 2.4 percent.[8] Candida species account for the majority of fungal infections in northern North America, with *C. parapsilosis* representing the most common isolate.[9] *C. parapsilosis* is typically less virulent than other yeasts like *C. albicans* and *C. tropicalis*, however *C. parapsilosis* has a particular propensity to adhere to prosthetic materials, which explains its increased pathogenicity in KPro patients.[10] Hypothetical risk factors for fungal infectious in KPro patients include prolonged soft contact lens wear and vancomycin prophylaxis,[11] although some series on fungal keratitis refute these findings.[12, 13]

When fungal endophthalmitis is suspected in a KPro patient, a vitreous sample is obtained via vitreous tap or pars plana vitrectomy, together with injection of broad-spectrum intravitreal antibiotics and an intravitreal antifungal—followed by initiation of systemic antifungals.[14-16] Although antifungal prophylaxis isn't routinely practiced for the management of KPro patients, Massachusetts Eye and Ear does recommend considering burst antifungal prophylaxis (amphotericin B drops, twice per day for a week every three months) in high-risk patients and geographic locations.[17]

In conclusion, endophthalmitis is a serious complication following KPro implantation. Fungal endophthalmitis should be considered in patients with persistent or recurrent retroprosthetic opacities or those associated with vitreous involvement. *C. parapsilosis* is a common infectious agent in KPro-related fungal endophthalmitis due to its propensity to adhere to the prosthetic surface. REVIEW

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

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

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

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

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

- Hypersensitivity *[see Contraindications (4)]*

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

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

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

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

Rare 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 *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation Day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

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

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

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

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

Manufactured for:
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One Health Plaza
East Hanover, NJ 07936

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

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

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

Indication

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

Important Safety Information

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

Please see Brief Summary of Prescribing Information on adjacent page.

References: 1. U.S. Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1. Accessed April 17, 2020. **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; November 2019.

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