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GEL DROP

Indications and Usage

• LO TEMAX® GEL is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery

Important Risk Information about LOTEMAX® GEL

• LO TEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures

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

• Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation

• Delayed healing—Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification

Please see brief summary of full prescribing information on adjacent page.

References:


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LOTEMAX®
loteprednol etabonate
ophthalmic gel 0.5%

INDICATIONS AND USAGE
LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION
Invert closed bottle and shake once to fill tip before instilling drops. Apply one or two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS
LOTEMAX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpetic keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

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

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

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

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

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

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

Contact Lens Wear
Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS
Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic Effects: Pregnancy Category C.
Loteprednol etabonate has been shown to be embryo toxic (delayed ossification) and teratogenic (increased incidence of meningeole, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥ 5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥ 50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥ 50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥ 5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX is administered to a nursing woman.

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment Of Fertility
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration
Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination
Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear
Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection
If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

FOR MORE DETAILED INFORMATION, PLEASE READ THE PRESCRIBING INFORMATION.

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Brief Summary: Based on full prescribing information.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
Regular aspirin use appears to be associated with an increased risk of neovascular age-related macular degeneration, and it appears to be independent of a history of cardiovascular disease and smoking, according to a report published online by *JAMA Internal Medicine*.

Aspirin is one of the most widely used medications in the world and is commonly used in the prevention of cardiovascular disease, such as myocardial infarction and ischemic stroke. While a recent study suggested that regular aspirin use was associated with AMD, particularly the more visually devastating neovascular form, other studies have reported inconsistent findings. Smoking is also a preventable risk factor for AMD, the authors write in the study background.

Gerald Liew, PhD, of the University of Sydney, Australia, and colleagues examined whether regular aspirin use (defined as once or more per week in the past year) was associated with a higher risk of developing AMD by conducting a prospective analysis of data from an Australian study that included four examinations during a 15-year period. Of 2,389 participants, 257 individuals (10.8 percent) were regular aspirin users.

After the 15-year follow-up, 63 individuals (24.5 percent) developed incident neovascular AMD, according to the results.

"The cumulative incidence of neovascular AMD among nonregular aspirin users was 0.8 percent at five years, 1.6 percent at 10 years, and 3.7 percent at 15 years; among regular aspirin users, the cumulative incidence was 1.9 percent at five years, 7 percent at 10 years and 9.3 percent at 15 years, respectively," the authors note. "Regular aspirin use was significantly associated with an increased incidence of neovascular AMD."

The authors note that any decision concerning whether to stop aspirin therapy is "complex and needs to be individualized."

"Currently, there is insufficient evidence to recommend changing clinical practice, except perhaps in patients with strong risk factors for neovascular AMD (e.g., existing late AMD in the fellow eye) in whom it may be appropriate to raise the potentially small risk of incident neovascular AMD with long-term aspirin therapy," the authors conclude.

Fetal Light Exposure Key to Eye Development

New research published in *Nature* concludes that not only does the eye depend on light to see, it needs light to develop normally during pregnancy.

Scientists say the unexpected finding offers a new basic understanding of fetal eye development and ocular diseases caused by vascular disorders—in particular retinopathy of prematurity. The research, led by scientists at Cincinnati Children’s Hospital Medical Center and the University of California, San Francisco, appeared online Jan. 16 ahead of print publication.

“This fundamentally changes our understanding of how the retina develops,” says study co-author Richard Lang, PhD, a researcher in the Division of Pediatric Ophthalmology at Cincinnati Children’s Hospital Medical Center. “We have identified a light-response pathway that controls the number of retinal neurons. This has downstream effects on developing vasculature in the eye and is important because several major eye diseases are vascular diseases.”

Dr. Lang is a principal investigator on the ongoing research along with project collaborator, David Copenhagen, PhD, a scientist in the departments of ophthalmology and physiology at UCSF. The scientists say their current study, conducted in mouse models, includes several unexpected findings.

"Several stages of mouse eye development occur after birth," says Dr. Copenhagen. "Because of this, we had always assumed that if light played a role in the development of the eye, it would also happen only after birth."

But researchers in the current study found that activation of the newly described light-response pathway must happen during pregnancy to activate the carefully choreographed program that produces a
healthy eye. Specifically, they say it is important for a sufficient number of photons to enter the mother's body by late gestation, or about 16 days into a mouse pregnancy.

Researchers were also surprised to learn that photons of light activate a protein called melanopsin directly in the fetus—not the mother—to help initiate normal development of blood vessels and retinal neurons in the eye.

One purpose of the light-response pathway is to suppress the number of blood vessels that form in the retina. These vessels are critical to retinal neurons, which require large amounts of oxygen to form and to function. When retinopathy of prematurity occurs in infants, retinal vessels grow almost unchecked. This continued expansion puts intense pressure on the developing eye and in extreme cases causes severe damage and blindness.

The research team led by Drs. Lung and Copenhagen conducted several experiments in laboratory mouse models that allowed them to identify the light-response pathway's specific components and function.

Mice were reared in the dark and in a normal day-night cycle beginning at late gestation to observe the comparative effects on vascular development of the eye. The researchers verified the function of the light response pathway by mutating an opsin gene in mice called Opn4 that produces melanopsin, in essence preventing activation of the photo pigment.

Both mice reared under dark conditions from late gestation, and those with mutated Opn4, exhibited nearly identical promiscuous expansion of hyaloid vessels and abnormal retinal vascular growth. The unchecked vascular growth was driven by the protein vascular endothelial growth factor. When the light response pathway is properly engaged, it modulates
VEGF to help prevent promiscuous vascular growth, according to researchers. The melanopsin protein is present in both mice and humans during pregnancy. Dr. Lang said the research team is continuing to study how the light-response pathway might influence the susceptibility of pre-term infants to retinopathy of prematurity and also be related to other diseases of the eye.

Blue Mountains: Early Predictor of Glaucoma Found

A new study finds that certain changes in blood vessels in the retina can be an early warning that a person is at increased risk for glaucoma.

Using diagnostic photos and other data from the Australian Blue Mountains Eye Study, the researchers showed that patients who had abnormally narrow retinal arteries when the study began were also those who were most likely to have glaucoma at its 10-year end point. If confirmed by future research, this finding could give ophthalmologists a new way to identify and treat those who are most vulnerable to vision loss from glaucoma. The study was recently published online by Ophthalmology.

The findings of the new study, led by Paul Mitchell, MD, PhD, of the Centre for Vision Research, University of Sydney, support the concept that abnormal narrowing of retinal blood vessels is an important factor in the earliest stages of open-angle glaucoma. Tracking nearly 2,500 participants, the study found that the open-angle glaucoma risk at the 10-year mark was about four times higher in patients whose retinal arteries had been narrowest when the study began, compared with those who had the widest arteries.

None of the participants had a diagnosis of open-angle glaucoma at the study’s outset. Compared with the study group as a whole, the patients who were diagnosed with OAG by the 10-year mark were older, had higher blood pressure or higher intraocular pressure at the study’s baseline, and were more likely to be female. Study results were adjusted for age, family history of glaucoma, smoking, diabetes, hypertension and other relevant factors.

“Our results suggest that a computer-based imaging tool designed to detect narrowing of the retinal artery caliber, or diameter, could effectively identify those who are most at risk for open-angle glaucoma,” said Dr. Mitchell. “Such a tool would also need to account for blood pressure and other factors that can contribute to blood vessel changes. Early detection would allow ophthalmologists to treat patients before optic nerve damage occurs and would give us the best chance of protecting their vision.”

Study Cautions on VEGF-Blocking Therapies

Increasingly aggressive therapies that block vascular endothelial growth factor could have a harmful effect on the ciliary body, according to a study in Investigative Ophthalmology & Visual Science.

“Very little is known about the factors that regulate the integrity and function of [the ciliary body] in the adult,” said author Patricia A. D’Amore, PhD, of Schepens Eye Research Institute/Massachusetts Eye and Ear. “Our finding indicates that VEGF-A is at least one of the molecules that play a role in keeping the ciliary body healthy and functioning properly.”

In the study, Expression and role of VEGF-A in the Ciliary Body, investigators simulated the VEGF-A activity in adult mice and found that blocking the protein decreased the intraocular pressure, an unexpected side effect that impaired the ciliary body.

Several anti-VEGF-A therapies are currently being widely and successfully used for the treatment of eye diseases like wet macular degeneration, diabetic macular edema and retinopathy of prematurity. Dr. D’Amore agrees that there is no evidence to indicate that the manner in which these drugs are being administered interferes with the ciliary body. “However, there is a move toward developing methods to continuously deliver anti-VEGF to the eye and to have drugs that are more potent inhibitors of VEGF,” she said. “I would be concerned that more aggressive VEGF inhibition in the eye would have deleterious effects on the ciliary body.”

The research team’s investigation of anti-VEGF-A on the ciliary body was the result of prior studies that found blocking VEGF can lead to the degeneration of capillary beds, particularly capillaries that have specializations called fenestrations like the ones found in the ciliary body. These include whole-body VEGF blockade in anti-cancer therapies that damage the capillaries of the kidney and the effect anti-VEGF has had on the thyroid function in people treated locally for brain tumors.

The results of the new IOVS study suggest further research, including clinical trials, should be considered. “I am hoping that revealing the possible negative side effects of VEGF inhibition in the eye will motivate research into new ways to block edema and blood vessel growth in the eye that does not require continuous inhibition of intraocular VEGF,” said Dr. D’Amore. REVIEW
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\(^*\)Posthoc analysis of combined data from two studies using a contralateral conjunctival allergen challenge (CAC). Based on a scale of itching scores of 0-4, with 0 as no itching and 4 as severe itching. Ocular itching was evaluated 3 minutes after allergen challenge at onset and at 16 hours. \(T(N=48; 95\% CI=48.8, 70.5)\) \(T(N=48; 95\% CI=48.3, 70.4)\)

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE:** PATADAY™ solution is a mast cell stabilizer indicated for the treatment of ocular itching associated with allergic conjunctivitis.

**DOSE AND ADMINISTRATION:** The recommended dose is one drop in each affected eye once a day.

**DOSE FORMS AND STRENGTHS:** Ophthalmic solution 0.2%; each ml contains 2.22 mg of olopatadine hydrochloride.

**CONTRAINDICATIONS:** None.

**WARNINGS AND PRECAUTIONS:** For topical ocular use only; not for injection or oral use. Contamination of Tip and Solution: As with any eye drop, to prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

**Contact Lens Use:** Patients should be advised not to wear a contact lens if their eye is red. PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% should not be used to treat contact lens related irritation. The preservative in PATADAY™ solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% before they insert their contact lenses.

**ADVERSE REACTIONS:** Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%. The following ocular adverse experiences were reported in 6% or less of patients: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus. The following non-ocular adverse experiences were reported in 5% or less of patients: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sininius, sinuins and taste perversion. Some of these events were similar to the underlying disease being studied.

**USE IN SPECIFIC POPULATIONS:**

**Pregnancy:** Teratogenic effects: Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 150,000 times the MROHD and rabbits treated at 400 mg/kg/day or approximately 100,000 times the MROHD during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/kg/day of olopatadine during organogenesis showed a decrease in fetal weight. Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus. Nursing Mothers: Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is administered to a nursing mother. **Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 2 years have not been established. **Geriatric Use:** No overall differences in safety and effectiveness have been observed between elderly and younger patients.

**NONCLINICAL TOXICOLOGY:** Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day or approximately 150,000 times the MROHD level. No mutagenic potential was observed when olopatadine was tested in an in vitro bacterial reverse mutation Ames test. In vitro mammalian chromosome aberration assay or an in vivo mouse micronucleus test, olopatadine administered to male and female rats at oral doses of approximately 10,000 times the MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of approximately 15,000 times the MROHD level.

**U.S. PATENTS:** Nos. 5,641,805; 6,995,186; 7,402,609

**REFERENCES:**

1. IMS Health. IMS National Prescription Audit™. August 2010 to September 2012. USC 61500 OPHT ANTI-ALLERGY.
2. Blaiss MS, Tort MJ. Zero itch in eyes treated with olopatadine 2.

**REFERENCES:**

1. IMS Health. IMS National Prescription Audit™. August 2010 to September 2012. USC 61500 OPHT ANTI-ALLERGY.
2. Blaiss MS, Tort MJ. Zero itch in eyes treated with olopatadine 2.
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When Multifocal IOLs Need Corneal Surgery

By Christopher Kent, Senior Editor

In many cases a refractive touch-up is necessary to satisfy these patients. Here’s help getting it right.

How to Do Biometry on the Table

By Walter Bethke, Managing Editor

Intraoperative aberrometry can help you get closer to your refractive target, experts say.

Survey: Refractive Surgeons Await Cross-linking

By Walter Bethke

Surgeons are eager to offer keratoconus and ectasia patients a new option.

Cover image: Mark Erickson, jirehdesign.com
Imagine the ability
to unlock new
treatment possibilities

Alcon is dedicated to developing pharmaceutical treatments for patients with glaucoma.

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The interface between physician practice and industry messaging, an untidy and changeable nexus at best, took a couple of interesting turns in recent weeks. The long-term implications are probably best left to the long-term, but they could be significant.

In early December, the U.S. Court of Appeals for the Second Circuit reversed a lower court ruling and held that the long-standing Food and Drug Administration prohibition on off-label marketing was a violation of manufacturers’ freedom of speech. This week, the agency announced that it would not seek an appeal, fearing, say some experts, that a loss would have national implications and throw the entire concept of FDA approval into question.

For example, why seek a time-consuming, expensive indication if you can get an easier one and then market it as you wish? If you can legally market off-label to physicians, then why not direct to patients?

The expectation is that there are better cases on which to make a stand making their way through the courts, and the government chose to limit the damage to the second circuit for the time being.

Off-label marketing of branded drugs is clearly attracting greater interest as more blockbuster drugs go off patent and potential generic replacements emerge. An FTC report this week found that 2012 saw the highest number ever of “pay to delay” settlements, in which patent-holders pay generic drugmakers not to develop or to delay marketing an authorized generic.

Against that backdrop, a Harvard University study published in January’s JAMA Internal Medicine finds that nearly 40 percent of the 1,900 surveyed physicians said they accede to patient demands for branded drugs even when a generic equivalent is available. Drug samples and meetings with pharmaceutical company representatives appeared to boost that rate, according to the study. The good news, say the authors, is that 60 percent of respondents say they resist such influences.

This month, the FDA made much of the launch of its new Medical Device Innovation Consortium, an independent, nonprofit corporation that will receive input from industry, government, and other nonprofit organizations. MDIC will prioritize the regulatory science needs of the medical device community and fund projects to help simplify the process of medical device design and pathway to market for these innovations.

Let’s hope it works, and that it may even serve as a model. Why not apply the same approach to the question of expanding the uses of approved pharmaceutical products based on scientific evidence instead of marketing hype, and to fill real medical needs instead of just additional sales opportunities?
A Look at What You Should Know in 2013

A new year brings regulatory issues and changes to diagnostic and CPT codes, reimbursements, incentives and more.

**Q** What Category I code changes were published with the 2013 Current Procedural Terminology manual?

**A** Several changes appear in the CPT 2013 manual, including new, revised and deleted codes. The new code is 64615 Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, trigeminal, cervical spinal and accessory nerves, bilateral (e.g., for chronic migraine). Report 64615 only once per session, and do not report 64615 in conjunction with 64612, 64613 or 64614.

The revised codes, with revisions underlined, are:
- 64612 Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (e.g., for blepharospasm, hemifacial spasm). (To report a bilateral procedure, use modifier 50);
- 65800 Paracentesis of anterior chamber of eye (separate procedure), removal of aqueous;
- 67610 Incisional biopsy of eyelid skin including lid margin;
- 99174 Instrument-based ocular screening (e.g., photoscreening, automated refraction), bilateral.

The deleted code is 65805, with therapeutic release of aqueous.

**Q** Were there any Category III code changes published in the CPT 2013 manual?

**A** Yes, there was one new Category III ophthalmology code implemented on July 1, 2012 and printed in the CPT 2013 manual: 0308T Insertion of ocular telescope prosthesis including removal of crystalline lens. Do not report 0308T in conjunction with 65800-65815, 66020, 66030, 66600-66635, 66761, 66825, 66982-66986 or 69990.

Additionally, the following Category III code was deleted in 2013: 0173T Monitoring of intraocular pressure during vitrectomy surgery.

Coverage and payment for Category III codes remains at carrier discretion.

**Q** Were there changes made to the relative value units of some ophthalmic codes in the 2013 CPT manual?

**A** Yes, a series of ophthalmic services were included in a review by the Relative Value Scale Update Committee. The following codes are examples of those reduced in their relative value units and the percentage of change from 2012:
- *Fluorescein angiogram* (92235)—6 percent;
- *IV injections* (67028)—9 percent;
- *Cataract surgery w/ IOL* (66984)—12 percent;
- *Complex cataract surgery w/ IOL* (66982)—25 percent;
- *Visual field* (92083)—29 percent;
- *Endothelial cell count* (92286)—70 percent.

**Q** Are there new drug codes pertinent to ophthalmology in the 2013 Healthcare Common Procedural Coding System manual?

**A** Yes, the 2013 HCPCS manual contains the following new codes: J7315—Mitomycin, ophthalmic, 0.2 mg and J0190—Injection, aflibercept, 1 mg. The J0178 code replaces the temporary code of Q2046 and will require two units on the claim form for appropriate reimbursement of the drug vial.

**Q** Were there any changes to diagnosis codes that require attention?

A new year brings regulatory issues and changes to diagnostic and CPT codes, reimbursements, incentives and more.
Preservative Toxicity Can Complicate Glaucoma Treatment

Preservative toxicity in glaucoma medications may complicate treatment. Eyes may present with subclinical fibres due to the cumulative effect of years of dosing with multiple preserved glaucoma eye drops. Preservatives can break the tight junctions in the apical epithelial cells in the cornea, with some cytotoxic activity, and impact the barrier function in the cornea. As cells start to be lost from the apical cornea, the ability of the cornea to hold the tear film diminishes. As the tear film becomes more unstable, the eye becomes dry and patients may complain of blurred and fluctuating vision.

While some clinicians will treat OSD in glaucoma patients by adding steroids or other anti-inflammatory agents, an alternative approach is the “subtractive strategy”—to take the patient off the preservative medications that may further exacerbate OSD symptoms.

Preservative-free glaucoma treatment is an established option in Europe where preservative-free beta blockers have been available for many years. Large epidemiologic surveys in Europe have shown the significant impact of switching to a preservative-free medication, or reducing the preservative load by switching out just the preserved beta blocker in patients on multiple IOP-lowering therapies. With the recent availability of new preservative-free glaucoma medications in the U.S., physicians have the opportunity to prescribe completely preservative-free medication regimens.

Preservative-free TIMOPTIC® (timolol maleate 0.5%) in OCUDOSE® (dispenser) is indicated in the treatment of elevated intraocular pressure in patients with glaucoma.

Preservative-free TIMOPTIC® in OCUDOSE® may be used when a patient is sensitive to the preservative in Timoptic (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

In patients being considered for add-on therapy after monotherapy with a prostaglandin analog, it makes sense to avoid adding to the preservative load. Preservative-free TIMOPTIC® in OCUDOSE® provides an option for adjunctive therapy when use of a preservative-free topical medication is advisable. When paired with a preservative-free prostaglandin, TIMOPTIC® in OCUDOSE® can be part of a truly preservative-free medication regimen.

IMPORTANT SAFETY INFORMATION
TIMOPTIC® in OCUDOSE® is contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of this product. This drug is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory or cardiac reactions, including death, have been reported following systemic or ophthalmic administration of timolol maleate. TIMOPTIC® in OCUDOSE® should be used with caution in patients with cerebrovascular insufficiency. The most frequently reported adverse experiences have been burning and stinging upon instillation.

REFERENCES

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OCU130-0612ROPH
WARNINGS

- mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients with impaired cardiac function, coadministration should be avoided.

Drug Interactions

Digitalis and calcium antagonists: The concomitant use of beta-blocker ophthalmic solutions with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time. CYP2D6 inhibitors: Potentially systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

- topical beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with topical timolol maleate.

- systemic beta-blockade is of concern when given to patients with asthma. Although bronchospastic reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, are rare in association with cardiac failure, have not received beta-adrenergic blocking agents, including Preservative-free TIMOPTIC in OCUDOSE.

- Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of asthmatic reaction; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure; (7) cardioneglect; or (8) hypersensitivity to any component of the product.

- Propranolol hydrochloride is contraindicated in patients with (1) Sneddon’s syndrome; (2) homocystinuria; (3) severe irreversible pulmonary hypertension.

- May be mutagenic in a range of in vitro studies with liver cell lines (100% of doses up to 100 mg/kg/day) but not at 5 or 50 mg/kg/day. At 50 mg/kg/day, there were no clinically meaningful changes in serum prolactin.

- Monkeys were devoid of mutagenic potential when tested in vivo (mice) in the micronucleus test and in vitro in a mammalian chromosome aberration assay (up to 100 mg/kg/day). At 100 mg/kg/day, there were no toxicologically significant increases in the incidence of micronuclei observed in mouse bone marrow. In rats, there were no toxicologically significant increases in the incidence of micronuclei observed in rat bone marrow.

- Increased incidence of mammary adenocarcinomas associated with oral timolol has been noted in association with administration of other beta-adrenergic blocking agents that do not share the structural and functional properties of timolol. In the absence of data from long-term studies in rodents, caution should be exercised in the use of topical timolol in patients with a history of breast cancer.

- Use caution when prescribing to patients with a history of bronchial asthma or a history of aspirin intolerance.

- Digitalis and calcium antagonists: The concomitant use of beta-blocker ophthalmic solutions with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time. CYP2D6 inhibitors: Potentially systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

- Concomitant use of beta-blocker ophthalmic solutions with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

- The incidence of pulmonary tumors was again observed at 500 mg/kg/day.

- In two-year studies with timolol maleate (up to 20 mg/kg/day) and in vitro in a mammalian chromosome aberration assay (up to 100 mg/kg/day), there were no toxicologically significant increases in the incidence of micronuclei observed in mouse bone marrow. At 100 mg/kg/day, there were no toxicologically significant increases in the incidence of micronuclei observed in rat bone marrow.

- In three basic experiments with timolol maleate (up to 100 mg/kg/day), there were no toxicologically significant increases in the incidence of micronuclei observed in mouse bone marrow. At 100 mg/kg/day, there were no toxicologically significant increases in the incidence of micronuclei observed in rat bone marrow.

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- Increased incidence of mammary adenocar
No new ICD-9 codes were published in the fall of 2012. This is due to anticipated implementation of ICD-10, which has been delayed until October 1, 2014.

**Q** What is the new Multiple Procedure Payment Reduction (MPPR) policy that went into effect in January?

**A** The MPPR policy reduces the technical component of the second and subsequent diagnostic tests by 20 percent when more than one diagnostic test is performed at one patient encounter on the same day by the same physician or group. The list of tests includes ultrasounds, imaging and visual fields. Tests that do not have a technical component (i.e., gonioscopy) are not subject to this policy.

**Q** Did ambulatory surgery centers and hospital outpatient department rates realize an increase to facility fees in 2013?

**A** For 2013, the Consumer Price Index and Multifactor Productivity Adjustment have updated the ASC conversion factor by 0.6 percent. HOPD rates increased approximately 1.8 percent for 2013.

**Q** What types of regulatory issues were identified as areas of concern for ophthalmology in 2013?

**A** The annual publication of the Office of Inspector General Work Plan identifies a series of items applicable to ophthalmology. Returning issues include: Place of Service Errors; Use of Modifiers During Global Surgery Periods; E/M Services Inappropriate Payments in 2010; Error-Prone Providers; Payments for drugs; Incident-To Services; Ambulatory Surgical Centers—Payment System; and Incentive Payments for Electronic Health Records.

New issues for scrutiny include: Ophthalmological Services—Questionable Billing; Modifiers GA/GZ/GY and appropriate use; Onsite Visits for Medicare Provider and Supplier Enrollment and Reenrollment; Hospitals—Acquisitions of Ambulatory Surgical Centers; and Impact on Medicare Spending.

**Q** Is the OIG still concerned about electronic health record documentation practices?

**A** Yes. The OIG says that it will continue to “review multiple E/M services for the same providers and beneficiaries to identify electronic health records documentation practices associated with potentially improper payments.”

**Q** When must professionals begin to utilize electronic health records to avoid penalties?

**A** Professionals must start using electronic health records in a “meaningful” way by July 1, 2014, and complete their meaningful use attestation for Stage One by October 1, 2014, in order to avoid penalties in 2015. (For more information, see “The Fundamentals of Meaningful Use” in the October 2012 issue of the Review.)

**Q** Are there changes to the electronic prescribing program for 2013?

**A** There are minimal changes. The bonus amount reduces to 0.5 percent, and some providers will be penalized for not meeting the participation requirement or qualifying for an exemption. The 2013 penalty is 1.5 percent on Medicare Part B allowed charges.

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.
The New Reality
Of the LensAR Laser

A novel way of looking at the anterior chamber may result in accurate femtosecond laser cataract surgery.

Walter Bethke, Managing Editor

Sometimes, looking at the world from a different perspective can allow a new understanding of how things work and help us solve problems in novel ways. LensAR has taken this concept to heart with its LensAR Laser System for cataract surgery, which uses a method called augmented reality to image a patient’s eye in an effort to provide all the information a surgeon needs to plan a femtosecond laser procedure. Here is a look at how the LensAR femtosecond laser system works in the cataract arena, and the possible benefits offered by a different view of the eye.

Augmented Reality

The LensAR’s augmented reality imaging system isn’t optical coherence tomography, but instead first uses a proprietary method to acquire biometric data and then uses ray tracing to create a 3-D eye model that the surgeon can see on the monitor.

“The laser has 3-D confocal illumination with the infrared camera,” says York, Pa., surgeon Denise Visco. “You get a Scheimpflug angle that produces a large depth of field within a single image, providing a high resolution and accurate imaging of ocular structures with very little image noise. If you have a dense lens, it can actually image through that accurately and locate structures such as the posterior capsule.” Since the system takes 10 images at different angles, the surgeon can rotate the 3-D eye image and see any lens tilt. Brookville, Pa., surgeon Louis Nichamin says this is important.

“It compensates for lens tilt,” he says. “This is important, as lens tilt may be one of the reasons complications occurred with early use of the femtosecond laser. Clinically, I do believe we are seeing this benefit, in that I’ve not yet had an incomplete capsulorhexis or breach of the posterior capsule since I’ve begun using the device in our clinic.”

The LensAR Procedure

As in other femtosecond cataract procedures, the first step of the LensAR procedure, docking, is key to success with the subsequent stages.

“With the LensAR platform, the surgeon first places the slim suction ring on the eye, typically without the use of a speculum,” explains Dr. Nichamin. “It doesn’t create a lot of pressure but nicely holds and fixes the eye. The surgeon then uses a joystick to center the docking element over the patient’s eye and lowers it into the suction ring. The surgeon checks the monitor to verify that the system has been lowered to the appropriate level and, because it’s a water interface, there is no corneal distortion that might lead to an error in imaging or laser energy delivery. The user then locks the docking window and is ready to go.”

Dr. Visco says that though the docking system works for most patients, it needs help when faced with a patient who’s carrying some extra weight around the eyes. “If someone has a fleshy orbit, his skin might come over the edge of the small suction cup,” she says. “On these occasions, the nurse has to gently hold the skin back as you perform the docking and get this small window piece connected. The company is supposed to have a new docking system in a couple of weeks in which they changed the position of where to lock the window so that it will be easier to access and lock.”

Though Dr. Visco says the Lens
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• Evaluate new technologies in diagnostic imaging
• Summarize the advances of ocular drug delivery systems
• List the risk factors for AMD and explain methods of screening and diagnosis
• Understand emerging issues in glaucoma: risk assessment, generic medications, progression and assessment of the optic nerve
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Program Times
Saturday, February 16, 2013
7:30am-4:30pm
Reception to follow
Sunday, February 17, 2013
7:30am-12:00pm

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AR system does a very good job of not creating tissue tags in the capsulotomy circle that would make it incomplete and hard to tear, she is still careful. “The only times I’ve noticed some issues with capsulotomy is if I have a particularly large patient and he’s breathing heavily,” she says. “I know his head is moving up and down while the laser’s running, so I make a mental note that there might be a tag. I believe that, even if a system is not supposed to create tags or features software that is supposed to reduce the incidence of tags to less than 1 percent, you still have to assume that every patient has a tag when you go in to operate, because it’s dangerous to assume that they don’t.”

She says that, when initially tutored on the capsulotomy step with the LensAR, she was told it would be best to put viscoelastic beneath the capsule and try to float it up. “I don’t like doing that at all,” she adds. “When I did that, I found I was chasing it all over the anterior chamber. Instead, I prefer to put viscoelastic on top of the capsule and then take a capsulorhexis forceps and draw the tissue toward the center from the periphery, making sure it’s completely detached. Then, when the capsule is bunched up in the center, you can just pick it up and remove it.

When it’s time to fragment the lens, the system allows the surgeon to choose a segmentation pattern. “I’ve traditionally been a phaco chopper, so my initial preference has been for a pie-cut pattern of four to eight nice, radial divisions during lens fragmentation,” explains Dr. Nichamin. “I’ve found that, in my hands, I don’t require too many division planes, but rather want discrete nuclear fragments that I can place my phaco probe on and remove. It’s clearly still a work in progress, but it’s fun; now we have a new tool with which to apply and refine our surgical techniques.”

Dr. Visco says going after the nucleus during a femtosecond cataract procedure will be different from what surgeons are used to. “It’s a bizarre experience when you first do it,” she says. “This is because there’s a lot of air in the eye and light refracting from inside the lens and reflecting because of the femtosecond cuts that have been placed in it. Every surgeon will figure out what works best for him or her. The nice thing is that the patterns can be customized to whatever you want. If you’re like me and prefer to use a flip, you can use a pattern that works a little better at augmenting what you’re doing.”

For the manual portion of the surgery, surgeons offer several tips. “First, it’s important to press down on the cataract to expel gas that may have collected under or around the lens,” advises Dr. Nichamin. “Then, thorough hydrodissection is performed. I continue to employ a cortical cleaving hydrodissection technique as described by I. Howard Fine in which the tip of the cannula is placed, dry, directly beneath the anterior capsule. This promotes mobilization of the cortical bowl. Early in my experience with the laser, while using prototypes abroad, I, like many other surgeons, found cortex removal to be more challenging. But since taking delivery of our laser, and using my own I/A instrument, I’ve not found cortex removal to be a problem. The instrument has an angled tip, with a custom made, enlarged aspiration port.”

Dr. Nichamin says that this instrument, which he has used for years to increase the speed and efficiency of cortical cleanup, will soon be commercially marketed specifically for femto-assisted cataract surgery, and that he has no financial interest in it.

Surgeons also say their LensAR systems have been able to fragment even very hard nuclei. “I’ve removed a light-perception cataract with it,” says Dr. Visco. “It has a very low cumulative dissipated energy during cataract surgery.”

Reimbursement

LensAR isn’t approved to perform corneal relaxing incisions to treat astigmatism, though Dr. Visco says the company has submitted its data to the Food and Drug Administration. Despite that, due to the recent ruling by the Centers for Medicare & Medicaid, surgeons using a femtosecond laser system to help accurately implant a premium refractive IOL, such as a multifocal, toric or accommodative lens, can bill the patient separately for the use of the femtosecond system’s advanced imaging technology, OCT or otherwise.

“CMS came to understand that there was a lot more to the technology, and recognized that the imaging aspect represented an entirely new facet of the surgery,” says Dr. Nichamin. “We are now able to image the anterior segment in a way that provides dramatically greater detail and information that may lead to better refractive results, specifically in conjunction with premium implants. As such, one can appropriately charge a patient for use of the laser when implanting a toric or presbyopia-correcting lens, or when performing laser-assisted corneal relaxing incisions.”

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When Multifocal IOLs Need Corneal Surgery

Christopher Kent, Senior Editor

In many cases a refractive touch-up is necessary to satisfy these patients. Here’s help getting it right.

Clear, fully accommodative vision may be the holy grail that ophthalmologists dream of providing their cataract patients, but that goal remains elusive. In the meantime, multifocal intraocular lenses remain a popular option for allowing good vision at both near and distance—at least in select patients.

Unfortunately, to produce good outcomes, multifocal IOLs require not only careful patient selection but also very precise refractive outcomes—meaning almost no spherical or astigmatic error. Given the challenges involved in achieving that level of precision today, doctors implanting multifocal lenses often need to compensate for the limitations of the surgery by adjusting the cornea preop or postop. In the United States, where toric multifocals are still not available, that often includes managing astigmatism.

“No matter how good your biometry or nomogram is, you’ll need to touch-up an eye containing a multifocal implant about 15 percent of the time,” says Richard Mackool Sr., MD, PC, director of the Mackool Eye Institute and Laser Center and senior attending surgeon at the New York Eye and Ear Infirmary, who has been implanting multifocal IOLs for 18 years. “I’m talking about routine, normal eyes, not eyes with strange biometries or excessive astigmatism. Fifteen percent of the time you won’t be within the ±0.5 D that satisfies 90+ percent of people. That’s because effective lens position is variable from person to person. Furthermore, K-readings are variable between machines and examiners, and probably between morning and night. These are factors you can’t control for.”

Here, several experienced surgeons share their thoughts on issues relating to this, including managing preop (and possibly postop) astigmatism; the importance of setting patient expectations; deciding whether any postop change is actually necessary; how long to wait before performing an adjustment; choosing the most appropriate corneal surgery to use; deciding whether to touch-up the cornea or exchange the IOL; and special circumstances that arise when doing both eyes in a short period of time.

Managing Astigmatism

Most astigmatism is addressed preoperatively or during the primary surgery in these patients. “The need for corneal correction of astigmatism with multifocal lens implantation is not uncommon, especially in the United States where we don’t have...”
toric multifocal IOLs yet,” notes R. Bruce Wallace III, MD, FACS, founder and medical director of Wallace Eye Surgery in Alexandria, La., and clinical professor at LSU School of Medicine and Tulane Medical School in New Orleans. Dr. Wallace says that multifocal implants have been a very important part of his practice since the 1980s; he favors the use of limbal relaxing incisions to manage astigmatism in this situation. “LRIs have been a mainstay of my practice for over a decade, and I’m very impressed with how well they work,” he says. “The results aren’t perfect, but they can get a patient to a situation where he’s comfortable with his outcome. I think LRIs will remain an important part of our practice, even after toric multifocals become available. They are a less-expensive option, especially for low levels of astigmatism.”

LRIs can also be made using the new femtosecond cataract lasers, increasing their accuracy significantly. “Our touch-up rate has been reduced by making arcuate incisions with a femtosecond laser at the same time as we perform the capsulorhexis and lens dissection,” says Richard J. Mackool Jr., MD, assistant director of the Mackool Eye Institute and attending surgeon at NYU Medical Center and the New York Eye & Ear Infirmary. “The laser has very accurate nomograms. We use penetrating limbal relaxing incisions as well. The femtosecond laser pays for itself because of the decreased reoperation rate.”

Dr. Wallace has also switched to making his limbal relaxing incisions using this technology. “Now that we have a femtosecond cataract laser, we can make them more precisely,” he says. “It’s also the only reason we can charge a patient for the use of the laser, at present.”

Of course, astigmatism can also be an issue postop, though this is less frequent. When it does arise, it raises additional questions. “If the patient has no spherical refractive issues but astigmatism is a concern, how you proceed may be a matter of doctor preference,” says James P. Gills, MD, founder and director of St. Luke’s Cataract & Laser Institute and clinical professor of ophthalmology at the University of South Florida. (His practice currently implants the Tecnis multifocal, and he frequently addresses issues in unhappy multifocal patients referred from other practices.) “In certain cases we use LRIs for small amounts of astigmatism; in other cases we use LASIK.

“However, if a significant amount of LASIK is required to correct astigmatism over a multifocal lens, some patients end up with a lot of glare, which upsets them,” he notes. “I’ve seen several of these patients, and it can be difficult to make them happy. This is especially true if you’re trying to correct hyperopic astigmatism. One reasonable alternative in the latter situation would be to consider a lens exchange, switching to a lens with more power, because myopic astigmatism is easier to address and might be managed with a relaxing incision.”

Dr. Mackool Sr., adds that some eyes simply are not good candidates for LRIs. “If you’re correcting pure astigmatism, meaning the spherical equivalent is close to zero, then you may want to address it with LRIs—unless you did LRIs before surgery either by blade or laser and the astigmatism remained,” he says. “In those cases, we find that you’re knocking your head against the wall. That cornea wants to heal in the same shape as it was before you made the incisions. So just bite the bullet and go to laser correction for those eyes.”

Setting Patient Expectations

Whenever patients pay out-of-pocket for a procedure, making sure their expectations are realistic becomes especially important. In the case of implanting a multifocal, that includes conveying the very real possibility that they will be among the 10 to 15
percent who end up needing a postop touch-up. “These patients have high expectation levels,” Dr. Wallace points out. “They may have friends who’ve had this procedure and are doing very well. Mainly, we want them to know that everything will not necessarily be perfect down the line, but we’re able to deal with that possibility. Explaining that to the patient ahead of time really helps.”

Dr. Mackool Sr. notes that it’s important to put this in writing. “Even if you do that,” he says, “80 or 90 percent of the patients who end up not seeing well because of a refractive error will come in and say, ‘I’m so disappointed.’ It doesn’t matter that you wrote it down. It’s human nature to hear what we want to hear and believe what we want to believe. So, you pull out the piece of paper and nicely explain that you did indeed warn them of this possibility.

“In fact, we give our patients dozens of pages of information to read,” he adds. “Not everything in there is immediately relevant to them, but much of it is. We find that patients who know more are more relaxed and confident as they go through this process—and the process can be difficult with a multifocal patient.”

“The other advantage of written materials is that they’re optional for the patients,” adds Dr. Mackool Jr. “Some patients who are very laid back may not read the materials. But many patients are very interested in being educated, and if you don’t give them accurate information, they’ll go to the Internet and come back with all kinds of questions from some website about the procedure you’re going to perform. Providing accurate information is far preferable.”

Dr. Wallace adds that it’s important to get the family involved in the preop discussion. “It’s very helpful to have family members present so that more than one person hears what you have to say about the procedure and its limitations,” he notes. “They won’t be surprised if everything isn’t perfect post-surgery. It also lets them know that we care about the patient’s welfare enough to be upfront about potential issues. You can also look at it as protection: having the family present helps in case the patient says, ‘I didn’t know this could happen.’ The family member will say, ‘No, they did tell you this could happen.’ But mainly, I think it helps maximize communication with the patient, and it helps the patient and the family trust us.”

Of course, no matter what the surgeon does to warn patients ahead of time, some disappointment may be inevitable. “After they’ve had the surgery, if the outcome isn’t ideal, we once again emphasize that we have a solution to the problem,” Dr. Wallace says. “Yes, it may take a while to get there, but we have a solution. That makes them feel a lot better. Of course, in some cases helping them might mean something as simple as a YAG laser treatment.”

Is Further Action Necessary?

Once the initial surgery is complete, a small amount of spherical refractive error can cause problems.

Of course, a central concern is knowing when to make the judgment call, since the healing process may cause the patient’s vision to shift for some time after surgery. “We usually wait about six weeks if we’re going to follow-up with LASIK,” says Dr. Gills. “A big factor in the final lens power is where the lens sits in the capsular bag. If the capsule shrinks, the anterior capsule may push the lens back, causing a small hyperopic shift. If the reverse occurs, you may get a myopic shift. So we wait at least six weeks to see what happens. We’d prefer to wait a year and a half, but the patients don’t want to do that.

“If the postop problem was simply a little astigmatism,” he adds, “we’d wait as long as possible and might ultimately decide to just do a relaxing incision.”

“We base how long we wait on stability, always,” says Dr. Mackool Sr. “Every refractive procedure should be based on that, whether it’s a touch-up after a multifocal implantation, LASIK on an eye that’s worn hard contact lenses for years, or an eye with astigmatic keratotomies whose effect is slowly disappearing. The more stable the eye, the more predictable the result. Some surgeons simply wait for three months, but if I had somebody
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whose refractive error at three months was different from their refractive error at two months, I’d have them come back at four months to see if it changed again.”

Dr. Mackool adds that the smaller the residual refractive error, the longer you should wait to do a touch-up. “When the error is small, small changes can occur that shift the patient from an unhappy camper to a happy camper, or vice versa, during that first six to 12 months,” he explains. “When we’re dealing with patients who are really on the fence, we explain to them that they are moving targets and we have to wait until they are as stable as possible. Patients are usually willing to accept that.”

Dr. Wallace notes that, besides giving the postop refraction time to stabilize, waiting before doing refinements also gives the patient time to adapt to the new visual system created by the multifocal lens. “Not only do patients not complain as much after two or three months, they actually see better,” he points out. “They notice fewer halos, and their mid-range vision gets better. So, patients are less likely to be asking for a lens exchange at that point.”

Once the patient’s vision has stabilized, Dr. Gills recommends using a contact lens to see whether any residual spherical error is really the source of the problem. “If a patient is having vision problems after multifocal implantation and the sphere is off by 0.5 to 0.75 D, put a contact lens on the eye, correcting for distance,” advises Dr. Gills. “If that clears up the problem, then go ahead and do laser correction. But always try the contact lens first. That will tell you whether other issues are interfering with the patient’s vision.”

Ultimately, he adds, your decision about whether to proceed with a touch-up should depend on the patient’s subjective opinion. “In most cases, if a multifocal patient has 0.75 or 1 D of astigmatism, you’ll have to correct that in order for the patient to be happy with his vision,” he says. “But if the patient is happy despite 0.5 or 0.75 D of astigmatism, trying to make the patient happier by correcting that astigmatism could backfire.”

**Don’t Be Fooled by PCO**

Another important issue when deciding whether or not a touch-up is warranted is to avoid being fooled by problems that can affect vision but won’t be resolved by a touch-up or lens exchange—in particular, posterior capsular opacity.

“It’s critically important that you determine the cause of the patient’s problem before attempting a touch-up,” says Dr. Mackool Jr. “For example, if the patient comes in after doing pretty well and says, ‘My vision isn’t as good as I thought it was,’ and you see a little refractive error, be sure there’s not a little bit of PCO. I don’t mean the kind of PCO that’s obvious; many times a small amount of PCO will have a large effect on a patient with a multifocal implant.”

“Toric lenses for six years. (He favors the toric ReSTOR +3 and +2.5, the Mplus Oculentis +3 and the Zeiss Lisa toric multifocal.) “I’m completely satisfied with the outcomes associated with these lenses,” he says. “I use toric multifocals if the patient has 1 D or more of cylinder, and I hardly ever perform LASIK after implanting them.

“In my hands, toric IOLs are more predictable than multifocal IOLs followed by LASIK,” he continues. “In my hands, LASIK variability exists when using multifocal IOLs simply because by definition we have multiple foci, not a precise focus. Many times you end up with a different refractive error even though the astigmatism is treated. For me, LASIK in this situation is less predictable than in normal patients, and much less predictable than simply using a multifocal toric IOL. I have never done a touch-up for the purpose of astigmatic correction following toric multifocal IOL surgery.”

Dr. Alio says the addition of toricity seems to have no negative impact on the overall quality of vision. “On the contrary,” he notes, “it is my impression that the patients have better vision than what you would expect following multifocal IOL implantation with LASIK as a touch-up. There are fewer complications and much more accurate outcomes.” He notes that rotation issues are the same as those encountered with monofocal toric IOLs. “Postop rotation is very unusual if you follow an adequate marking and implantation protocol,” he says. “Modern lenses do not rotate at all—or very little—in the bag.”

Dr. Alio notes that his patients are happier with these lenses. “The shorter follow-up is better for everybody,” he says. “The patient’s vision is much better from the beginning and the patients are discharged earlier. These lenses do increase the cost to the patient by about 20 percent, but if properly explained, this is well compensated by the many advantages that are found in the use of these lenses.”

---OK---
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has solved their problem. So before you go to corneal laser treatment, it’s a good idea to make sure there is no PCO. If there is, laser that first. You should definitely have a lower threshold for doing a YAG on one of these patients.”

The senior Dr. Mackool agrees. “The key in this situation is that they used to be happy, but now they’re unhappy,” he says. “If you’ve got a patient who had glare from the get-go, and you try to talk yourself into seeing a little PCO, think twice: That may be a person who has multifocal-induced dysphotopsia. If you do the YAG, even though the patient was never happy from the start, you may come up against the rare need to exchange the IOL. Now you have an open capsule, which changes the whole scenario. The risk factors are still manageable, but there’s no denying that you’ve increased them.”

He adds that one way to eliminate the likelihood of being fooled is to check the posterior capsule shortly after surgery and get the patient to tell you how he’s doing at night. “If you don’t pin the patient down, sometimes they’ll come in a year or two later with some complaints, and they won’t be able to tell you when the problem started,” he says. “You might have been able to pin them down if you talked to them shortly after the procedure, but a year or two later either their memory is not so good, or they never paid attention because no one was asking them to. Then you have some trickier decisions to make.”

**Which Corneal Surgery?**

Many surgeons today would automatically choose LASIK if a corneal touch-up was felt to be necessary, but arguments can be made for using PRK or even radial keratotomy instead. Dr. Wallace prefers to use LASIK. “Some surgeons prefer PRK in this situation, but in our hands, LASIK provides faster healing and less discomfort,” he says. However, he notes that dry eye can change that. “We had a patient this week who would have benefited from LASIK, but has such a severe dry-eye history—he’s been on Restasis and has had punctal plugs—that we’ve opted for doing an LRI initially for the astigmatism. After the cataract surgery we’ll determine what the spherical refractive error is, and then maybe do a two- or four-incision radial keratotomy.”

Both Drs. Mackool favor using PRK for touch-ups instead of LASIK. “Initially we did LASIK on top of multifocals, but we found that we’d lose a line or two of BCVA,” says Dr. Mackool Sr. “It’s true that the patient’s visual acuity would usually recover over a period of six to 12 months, because the cornea remodels its epithelium to reduce higher-order aberrations over time—at least if the higher-order aberrations aren’t too bad. But why put the patient through that if you don’t have to?”

“Most patients in this situation only need a very small correction—a diopter or less of sphere and/or cylinder,” he continues. “So, they’re really ideal candidates for small PRKs. When you start doing LASIK in this situation—and I don’t care whether you make the flap with a femtosecond laser or a microkeratome—asking the cornea to heal absolutely perfectly is asking a lot. And increasing higher-order aberrations in this situation is a recipe for the patient to say, ‘I really don’t like my overall quality of vision’.

“So, our current recommendation is to do small-treatment PRKs,” he says. “We find that we don’t lose BCVA even transiently using that protocol. Yes, it takes the patient longer to get to his best vision, maybe a month. And some of them, maybe 25 percent, will have some discomfort for a day or two, maybe even pain, but that’s controllable with meds.”

He adds that in this situation he uses mitomycin-C. “We use mitomycin for a minimum of 60 seconds, regardless of the extent of the treatment,” he explains. “There have been reports in the literature of successfully doing this with 10 or 20 seconds of mitomycin, but we had some instances of haze with small treatments. That’s pretty frustrating.”

“We see virtually no haze [with our current protocol],” adds Dr. Mackool Jr. “It’s much safer, and there’s really no downside to it.”

Of course, some surgeons would hesitate to use PRK for fear that patients would complain about the discomfort. However, Dr. Mackool Jr. notes that patients don’t complain as long as they’re fully educated before the surgery. “When patients are prepared for what you’re going to do, they tolerate it extremely well,” he says. “They expect to have the bandage contact lens in for a week, and they understand that their vision will improve over time. We don’t get any complaints in those circumstances. It’s only when patients don’t know what to expect that these things become an issue.”

**Touch-up or Exchange?**

Occasionally a patient will have a more serious refractive surprise after multifocal IOL implantation. In that case, the surgeon has to decide...
whether a lens exchange would be a better option than a corneal refractive procedure.

Dr. Wallace says that, faced with a need for postoperative adjustment, he prefers to avoid exchanging the implant. “There are two reasons for that,” he notes. First, it’s more surgery and work inside the eye. Second, we want to wait to make sure that the refraction is stable before we do anything to change it; it might improve on its own. So, we like to wait at least three months before we make any sort of refractive change on an eye that had a refractive surprise following a multifocal implant. That, in turn, adds to the impetus to avoid exchange, because after three months it’s riskier to exchange an IOL, compared to, say, three weeks postop.

“Basically,” he continues, “we wouldn’t exchange a lens because of a refractive error unless it was something that we couldn’t correct on the cornea. If the patient has significant dry eye or is hyperopic, that might require a lens exchange, but that’s not common at all in our practice.”

Dr. Gills says the extent of the refractive surprise is a key factor in his decision. “If a refractive surprise was 1.5 D, a lens exchange would be my first choice, but we could certainly do LASIK as well,” says Dr. Gills. “If the surprise was greater than 1.5 D, I’d prefer to go with a lens exchange. I like to see as little corneal change as possible.”

Dr. Mackool Jr. agrees. “Basically, you only want to do laser correction for small refractive errors,” he says. “For large refractive errors, which are usually caught early on, it makes more sense to do an IOL exchange.”

“If you start doing laser correction of even moderate errors, you’re going to be creating more higher-order aberrations on the cornea,” adds Dr. Mackool Sr. “If you add those on top of a multifocal, the patient’s vision will suffer.”
Occasionally, other circumstances will make a lens exchange impractical. "Suppose I put in a capsular tension ring to address zonular laxity during the primary procedure," says Dr. Mackool Sr. "I've done this many times with good results. But once in a while this type of eye may toss a refractive error problem at you because it has an unpredictable effective lens position. In that case, I'd be gun-shy about going in to do an exchange. I'd be far more likely to fall back on laser correction."

Creating a Safety Net

Not surprisingly, many surgeons prefer to avoid lens exchange because of the difficulty of the procedure. However, Dr. Mackool Sr. notes that he and his colleagues have developed a surgical technique that can be used during the primary surgery that makes a lens exchange far less difficult, should it need to be done.

"We reported on this technique about five years ago," he says. "When we put in multifocals, we remove the epithelium from beneath the anterior capsule. Those cells release certain chemical agents such as fibronectin that cause the anterior capsule to adhere to the optic of the lens, typically three to four weeks postop. Removing these cells delays adhesion between the anterior capsule and the lens and haptics, allowing for much easier lens exchange many months postop, should that become necessary."

Dr. Mackool Jr. agrees. "It's usually the myopic eyes with large bags that have rotation of a toric lens," he points out. "Some surgeons remove the epithelial cells from the anterior capsule on every cataract patient, and they haven't reported any increase in toric rotation. There was a report from Japan that removing the epithelium from the anterior capsule resulted in earlier PCO, but we haven't seen that."

"In the meantime, the fact that the lens doesn't adhere to the capsule so quickly removes the urgency of managing a possible lens exchange," he concludes. "If a patient comes in complaining of glare in the first eye, I tell him we should wait and see what happens before we proceed. I know I can exchange the lens at six months, if necessary. The risk won't be any greater at that point in time. Of course, the majority of these patients don't end up getting an exchange. They come to grips with the glare issue."

When Doing Both Eyes

Often a surgeon will do both eyes in sequence, raising a few special considerations. First of all, Dr. Mackool Jr. notes that in this situation it's important to operate on the nondominant eye first. "A patient can potentially tolerate a little bit of glare and halo in the nondominant eye and still get the benefits of reading vision," he points out. "So you haven't lost much if you put a multifocal lens in one eye but have to change your plan and put a standard aspheric implant in the other eye."

Also, it's important for the patient to provide key information about the outcome in the first eye, as this will potentially impact how you treat the second eye. Not surprisingly, patients may not provide that information unless you specifically ask them to. "We wait two weeks before doing the second eye," notes Dr. Mackool Jr. "We tell every patient, 'Don't worry about your vision during the first week. But during the second week, before you have the other eye done, pay attention to how much glare you have; test the eye at night.' If they're going to have trouble, you want to find out about it before you do the other eye."

When patients are referred in from other practices, we often find that the surgeon put in one lens and then automatically put the other one in without really checking to say whether the patient had any complaints. At least one in 20 patients will have glare or halo that's bothersome, and you don't want to proceed with the second eye if that's the case."

Dr. Mackool Sr. notes that the self-testing must be monocular. "Some people can be blind in one eye and not notice it, so they certainly can overlook glare in one eye," he observes. "We've had patients come in complaining of glare in both eyes, insisting that they didn't have the glare problem until
the second eye was done. Of course, they did, but for whatever reason, they relied on the other eye and weren’t bothered by the glare as a result. So after the first eye is done, the patient needs to check for glare in that eye, by itself. And this should be included in the literature that you give the patient as well.”

Multifocal Touch-up Pearls

• Don’t exceed the astigmatism you can treat. “If the patient has more than 2.5 to 3 D of astigmatism, we would discourage multifocals altogether,” says Dr. Wallace. “There is only so much astigmatism you can correct with LRIs or LASIK. Of course, those limits are likely to change when toric multifocals become available.”

• Include potential touch-ups in the up-front cost. “People like to pay for a complete job, and you need to deliver it,” notes Dr. Mackool Sr. “Making sure the cost is covered is important if you want your practice to run as smoothly as possible.”

• Make LRIs a little more peripheral for a multifocal patient. “LRIs are really corneal relaxing incisions, and you don’t want to interfere with a LASIK flap, should LASIK become necessary,” says Dr. Wallace. “For that reason we’re typically a little more peripheral when it comes to doing limbal relaxing incisions for patients that are receiving multifocals.”

• See the patient monthly during the initial postop period. “During the three-month period when we’re waiting to see whether a postop treatment will be necessary, we have the patient come in every month,” says Dr. Wallace. “This accomplishes several things. First, when a patient has vision trouble after surgery, it’s possible that the patient is bothered as much by tear dysfunction in that eye as by any refractive-error issues. Seeing him every month allows us to monitor the patient’s tear function and do whatever we can to support it.”

“Having him come in also allows us to look for a trend in the postop refraction,” he continues. “And, it shows the patient that we care. That’s important because these patients are typically not really happy. They paid out of pocket for a better result than they’re having. Seeing them every month shows them that we’re staying on top of their situation and doing what we can to make it better.”

• Don’t proceed with a touch-up unless any dry eye has been addressed. “This can be a huge issue,” notes Dr. Mackool Jr. “Some patients who didn’t have dry eye preop develop it postop as a result of using multiple drops. Don’t hesitate to put these patients on a lubricant or punctal plugs, or both. Dry eye can produce almost any kind of refractive error—cylinder, myopia, hyperopia, variability. So get rid of the dry eye before proceeding.”

• Remember that reading problems are often related to pupil size. “At least once a month I see a patient with a ReSTOR implant and good distance vision but difficulty reading,” says Dr. Mackool Jr. “The surgeon who implanted the lens is perplexed and the patient is too. It turns out that all the patient needed was a smaller pupil to read. The functionality of the lens for reading improves if the pupil is less than 3.5 mm in size. If they use a dilute pilocarpine solution when reading, their problems go away. It also eliminates a lot of distress if you warn patients in advance about this possibility.”

Dr. Mackool Sr. notes that this problem isn’t limited to the ReSTOR lens. “I’ve seen the same problem with other diffractive multifocals,” he says. “It turns out that a certain accommodative pupil diameter is optimal. If you don’t have that, you’ll tend not to do as well with the various lenses for near vision. It’s just the way it is. Of course, it would help if surgeons measured pupil diameter when deciding whether a patient is a good multifocal candidate, but I’m not sure that surgeons always do this.”

• Only use a piggyback lens as a last resort. “The piggyback on multifocal question is controversial because we don’t have a lot of data,” notes Dr. Mackool Sr. “No one has done a huge series of those. But suppose I had a patient who couldn’t have laser vision correction because of dry eye or keratoconus. Suppose he has a multifocal in there and a refractive error and he’s miserable, and suppose I don’t want to exchange the lens because I think the zonule might be lax.

“Would I do a piggyback lens in that situation?” he continues. “Yes, I would. I’ve seen a few done. But I’d tell the patient in advance that we don’t have a lot of data on it, and he might not like the quality of vision it produces—although I suspect in most patients it wouldn’t harm their quality of vision. Also, it’s relatively easy to remove a piggyback lens, although then you’re back to square one. Fortunately those situations are pretty rare.”

“...
In some ways, selecting an intraocular lens for cataract surgery is like jumping into a lake before you know its depth—and you never really know for sure until you break the surface, or, in the case of surgery, until the lens is in position postoperatively. Several companies and researchers, though, are working on ways to help surgeons home in on the right lens power during the surgery itself—before they make the leap and choose a lens—in order to reduce the number of astigmatic or refractive surprises postop. Here, cataract surgeons and intraoperative aberrometry developers explain the current state of the art, as well as how you can get the best results if and when you decide to use such a system.

WaveTec Vision’s ORA

The Optiwave Refractive Analysis system is the only intraoperative aberrometer available for sale in the United States. The device attaches to the operating microscope and can be used for aphakic refractive measurements to help choose the proper lens, and for pseudophakic measurements to help rotate toric IOLs to the proper axis as well as to view the effect of limbal relaxing incisions as they’re created, giving the surgeon a chance to enhance the cuts for greater effect.

“In a way, it’s a form of intraoperative biometry,” says Clearwater, Fla., surgeon Robert Weinstock. “It’s a useful tool in helping the surgeon select the correct lens power, whether it’s a standard cataract surgery, a toric lens implantation or a complicated case involving a patient who has had previous refractive surgery. In all these situations, the device can either confirm or deny the chosen preop lens power and give the surgeon a suggestion as to what might be a good choice for the eye. It provides another value-added piece of information in these cases.”

Several years of experience with WaveTec’s systems, starting with the original ORange, have taught surgeons certain techniques to make the most of the measurements.

“You want to make sure the cul-de-sac is clear and the lid speculum isn’t pressing on the lid or orbit,” explains Venice, Fla., ophthalmologist P. Dee Stephenson. “You want to ensure the cornea is moist and clear, the pressure is stable and that the patient isn’t looking down, but is instead looking superiorly.” Surgeons also say topical anesthesia is a must because they need the patient to stare at a fixation light during the measurement. “You also want the microscope position fairly coaxial, so there isn’t much tilt of the...
scope and it’s aligned perpendicular to the patient’s eye,” says Dr. Weinstock.

To proceed with the aphakic reading after the cataract has been removed, Dr. Weinstock first uniformly fills the eye with cohesive viscoelastic. “When I see the viscoelastic start to prolapse out of the wounds, it means I’ve filled the entire capsule and anterior chamber with it,” he notes. “Then seal the globe and check the pressure to make sure it’s between 18 and 30 mmHg. That’s when I know I’m going to get a good reading. There’s a camera image of the eye in which you can see the Purkinje reflexes, and a fringe-pattern image that gives a qualitative analysis of the quality of the tear film. If the tear film is irregular, the fringe pattern won’t look good or will be distorted. In these cases, you can sometimes squirt some more BSS on the cornea to improve the surface. With the patient fixating on the light, my assistant presses the touch screen to capture the image. It captures 40 images in five seconds or less, and then in 10 seconds or less it processes the information. It then displays the refraction and the suggested lens power. I compare that to what my preoperative lens selection was, based on preop biometry. I will also look at the preop cylinder versus that which was measured and use that as a guide to how accurate the readings are.

“Every patient is brought into the OR with four or five IOLs, usually 1 or 2 D above and 1 or 2 D below the IOL power we selected preoperatively,” Dr. Weinstock adds. “For a post-LASIK patient, we bring in with IOLs up to 3 or 4 D above and below the projected power. No patient has the lens package opened until the intraoperative biometry is done, the data’s analyzed and compared to the preop data, and a final decision is made. Then the lens is opened and placed on the table.” Dr. Weinstock says in many cases the actual power needed as identified by ORA is more than 0.5 D different from the preop one that was identified, and can be off by 2 D or more in someone who has had previous refractive surgery.

An aphakic measurement also helps with limbal relaxing incisions, surgeons say. “When you remove the cataract, there might be more or less astigmatism than expected,” explains Dr. Stephenson. “The beauty of using ORA is, once the patient is aphakic, you do a measurement and you know how much astigmatism the cornea itself has. You can then titrate the amount of correction with an incision. For example, if you decided you were going to do two LRIs with 30-degree arcs at 600 microns and the ORA reading tells you that the astigmatism is reduced, that’s great. But if it’s not, you can enhance the incision—and always go deeper before you go longer.”

Dr. Stephenson says there are functions to help manage astigmatism with lenses, as well. “With a toric implant, the ORA readings show the amount of astigmatism, what you could expect to correct, the axis, and how much astigmatism would remain if you were to implant a certain lens power,” she says. Surgeons say there are times when the measurements will make them take a step back and evaluate things before proceeding. “There’s some thought that goes into it, it’s not a device for which you just accept the reading at face value,” says Dr. Weinstock. “It’s no different than doing an IOLMaster and comparing that measurement to the Lenstar, or doing a Lenstar and comparing it to immersion. It’s another data point to use in decision making. Sometimes, you’ll get a reading that is way off, where the IOLMaster and immersion say one thing, but the ORA is, say, 3 D different. If this happens, I’ll go back and make sure the speculum isn’t pushing down on the globe, or that there’s not a dry area on the cornea, and then repeat the measurement. However, some eyes are just unusual. RK eyes are very sensitive to changes in IOP, and their corneas can have really unusual shapes. Actually, RK eyes are the ones I find to be least reliable on the ORA. There have also been readings that don’t make sense altogether and it turned out that, for one reason

The ORA system performs intraoperative measurements in order to allow surgeons to get as close as possible to the ideal intraocular lens selection before they close the case.
Dr. Weinstock recalls one case where there was a significant difference between the ORA reading and the preop biometry. “In a patient who had had previous myopic LASIK, the ORA said 21 D for the power but the two other measurements that we did preoperatively, the IOLMaster and immersion, both recommended an 18-D lens,” he says. “So I went back and looked at the preop data, what K values were used for that, and it turned out we used the IOLMaster Ks for the IOlMaster reading and the manual Ks for the immersion. When I looked at the Ks from the Nidek OPD, they were much flatter than the ones we used in those formulas, so it led me to believe that our manual and IOLMaster Ks weren’t accurate. Looking at the patient’s history, she was a -6, but there was only a 4-D change on the keratometry based on these readings, except for the Nidek OPD. It turns out that the real Ks were much flatter than the ones measured preoperatively, and we would have been 2 to 3 D off if we didn’t use the ORA.”

To help increase the accuracy of its calculations, the ORA employs a feature called the WaveTec AnalyzOR, which accumulates the data from all ORA users in an effort to hone the system’s lens calculations. “Part of this is analysis software that lets you track your own outcomes, to see how close you are to your targets, how you’re doing, and to develop your own personal nomogram in ORA,” says Dr. Weinstock. “The machine is also connected to WaveTec, and they take the global data and, based on that, they perform software updates to each unit that will change some of its proprietary formulas and surgeon factors both individually and globally. The company will get an overall look at the outcomes for all users using a particular lens, for example, and it can adjust its formulas based on that data in order to refine them.”

In terms of its use in their practices, Drs. Weinstock and Stephenson don’t use ORA on everyone, just on patients who have upgraded to a premium surgical package, for whom it’s an extra charge. “It’s improved my outcomes,” says Dr. Weinstock. “Our numbers show that, about 60 percent of the time, the ORA results in my using a lens power that’s different from what I would have selected based on preop measurements. Even though in many cases I’m only changing the lens power by 0.25 or 0.5 D, it’s dialing me in that much closer.” Dr. Stephenson says she’s tracked her improvement with different lenses. “Using ORA when implanting certain lenses has improved my accuracy. For instance, in my practice, with the Akreos lens, 92 percent of patients are within 0.5 D and 71 percent are within 0.25 D of the intended target. So, the results are as good if not better than LASIK’s. And with the new enVista lens, 96 percent of my patients are within 0.5 D and 73 percent are within 0.25 D. By entering my postops in WaveTec’s AnalyzOR, I’ve been able to personalize my surgeon factor and optimize my outcomes. I follow my outcomes closely and have raised the bar for my practice.

“For me, intraoperative aberrometry is a must,” Dr. Stephenson continues. “Patients today, especially baby boomers, want perfection, and ORA gives me the confidence to know I am giving my patients the best visual outcomes.”

**Products in the Pipeline**

On the horizon, there are a couple of groups working on new devices, each with its own approach to intraoperative aberrometry.

Clarity Medical Systems’ HOLOS IntraOp is a system designed to be mounted on the surgical microscope and used to produce continuous refractive data.

David Chang, MD, clinical professor at the University of California, San Francisco, has worked with Clarity on the HOLOS, and explains the device’s unique approach. “Current clinical wavefront measuring devices are based on Hartmann-Shack or Talbot-Moiré technology—which were originally developed for astronomy,” he says. “HOLOS incorporates an entirely new wavefront measuring technology that was specifically developed for the optical axis of the eye. This optimization shortens the time for data acquisition and analysis to an enormous degree. The result is that data can be continuously measured and displayed in real time. Comparing HOLOS to its predecessors is a bit like comparing a still camera to a video camera.”

What the surgeon sees during the operation will be “akin to a real-time refractive movie,” says Barry Linder, MD, Clarity Medical Systems’ chief medical officer. “He or she will be getting the sphere, cylinder and axis continuously. The surgery can also be reviewed post-surgery, with the system’s DVR capability. A higher-order aberration display won’t be part of the initial product, but is a capability of the HOLOS technology platform.”

In the final, finished product, the company says the HOLOS intraoperative monitor display will consist of three main elements: quantitative on page 67)
Q: When implanting multifocals and achieving 20/20 distance, J1 near why do I still have some unhappy patients?

A: Unless you are able to determine the smallest aberration in the lens and the cornea you will always risk having unhappy patients. It is essential that your diagnostic equipment can measure these important parameters in assessing your patient’s total visual system.

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Surgeons are eager to offer keratoconus and ectasia patients a new option.

When surgeons discover a better way to treat their patients—especially when the option is backed by research—they’ll gladly adopt it in their practices. This seems to be the case with corneal cross-linking, which, though unapproved, promises to be a popular option when it becomes available for many of the surgeons on Review’s refractive surgery e-mail survey, with 51 percent of them saying they’re very interested in doing it. They say it might be a more lasting solution for keratoconus sufferers, and help patients who don’t have a lot of options.

These are just some of the findings from this month’s e-mail survey on refractive surgery. The survey e-mail was opened by 1,400 of 10,000 subscribers to Review’s electronic mail service (14 percent open rate), and of those, 67 surgeons (5 percent) responded. Here’s what they had to say.

Cross-linking Draws Attention

Surgeons appear to like what they’re hearing about this option for keratoconus sufferers and those with post-LASIK ectasia. In addition to the 51 percent who are very interested in cross-linking, 37 percent say they’re somewhat interested in it. Sixteen percent say they’re not interested in it. “I’m already using it as part of an...”

**Procedure Used for Most Cases**

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FDA clinical trial, and I’m very happy with the results,” says Gregory Parkhurst, MD, of Houston. “It appears to be standard treatment for corneal ectatic disease internationally and will likely become so in the United States after approval.” Cristobal Mendez, MD, of San Juan, Puerto Rico, is looking forward to giving the procedure a try. “I have a large number of keratoconus patients—more than 5,000!” he says. “And this procedure might give them a permanent solution that at this stage I don’t have.” A surgeon from Texas says he is very interested in it “in order to get better results in patients with hyperopia and to do thinner/former fruste cases.” Albuquerque, N.M., corneal specialist David Bentsisly, MD, is cautiously optimistic, and likes cross-linking’s potential. “As a corneal specialist I see lots of KC and would like some option other than transplant, RGP’s and Intacs,” he says. A surgeon from North Carolina, though, says he’s not interested in cross-linking because he “doesn’t see enough of these patients to make it worthwhile.”

**Volumes and Procedures**

In terms of the procedure surgeons say they use for the majority of their cases, 39 percent choose custom LASIK, 25 percent use conventional LASIK, 18 percent like PRK, 5 percent do epi-LASIK and 2 percent perform clear lens extraction and monofocal intraocular lens implantation. As for LASIK volume, 34 percent of respondents perform between five and 20 cases per month, 28 percent do 21 to 50 and 19 percent do fewer than five. On the high end, 13 percent perform 51 to 75 cases, 2 percent do 76 to 100 and 4 percent do more than 100 cases each month. The average per-eye charge for LASIK reported on the survey is $2,545.

When faced with a patient on the high end of myopia,
-11 D, 71 percent of the surgeons say a phakic IOL is the best choice. Nineteen percent say they’d do LASIK, 10 percent like PRK, 5 percent prefer LASEK and another 5 percent would use CLE/IOL.

Dr. Parkhurst thinks the phakic lens is a good option. “The refractive effect is more predictable when compared to LASIK/PRK,” he avers. “There’s also no worry about inducing aberrations from a large corneal ablation. Vision quality has been proven to be superior to LVC in these patients, and it’s easier to calculate the IOL power in the future when it’s time for cataract surgery. When compared to CLE, I prefer phakic IOLs for high myopia because there has not been a significant rate of retinal complications either in surgeons’ clinical experience or in FDA clinical trials. There is higher risk of retinal tear with and without detachment when the volume of the crystalline lens is removed and replaced with a synthetic IOL, particularly in high myopes with long axial lengths.”

For the +2 D hyperope, LASIK is the most popular option, chosen by 82 percent of the respondents. Thirteen percent like PRK, 8 percent prefer LASEK, 5 percent would do CLE/IOL and 3 percent would pursue another option. “LASIK for +2 D in young hyperopes is very safe and effective,” says Dr. Parkhurst. “In older hyperopes, the higher the hyperopia and the older the patient, the more I lean toward CLE/IOL. It depends on age. If the patient’s young, then LASIK. If the patient’s post-presbyopic or has early, non visually significant cataract formation, I prefer CLE/IOL.”

For the 45-year-old hyperopic presbyope, surgeons’ preferences varied greatly. Twenty-six percent prefer LASIK monovision and 13 percent each like multifocal contact lenses and CLE/ReSTOR implantation (see graph, this page). “LASIK monovision is easy and well-tolerated,” says one refractive surgeon. Dr. Bernitsky says the choice would depend on the quality of the ocular surface. “Some 45-year-old hyperopes are actually fine for monovision LASIK,” he says. “However, if the patient has any degree of dry eye, early lens changes, steep corneas or hyperopia greater than or equal to +3 D, CLE is better.”

For the myopic presbyope, 62 percent of surgeons prefer monovision LASIK, 13 percent like bifocals, 13 percent prefer multifocal contact lenses, 8 percent choose contact lens monovision, 5 percent would do CLE/Tecnis implantation and 3 percent would choose CLE/ReSTOR. Though Dr. Parkhurst says LASIK monovision would be his first choice, he could see situations where lens-based procedures might be better. “LASIK monovision is safe and effective in patients who have successfully adapted to monovision contact lenses,” he says. “CLE with either the ReSTOR...
or Tecnis multifocal is a reasonable option depending upon the rest of the history, the level of myopia and the health of the cornea versus the health of the crystalline lens. I’d use a modified monovision approach with Crystalens if there were structural or optical issues with the cornea that might disrupt safe LASIK and/or multifocality.”

When LASIK Falls Short

When surgeons have to go back and enhance an eye that has had LASIK, 57 percent prefer to lift the flap and ablate the bed. Forty-six percent leave the flap down and ablate the surface, and only 2 percent will recut the flap before ablating. “I’ll relift the flap if it’s been less than three years since the first procedure,” says Woodway, Texas, surgeon George Walters, “because the surgery is tolerated well if care is taken to avoid epithelial ingrowth.” Other surgeons feel similarly, though the postop period varies. Los Angeles surgeon James Salz says that he prefers flap lift “during the first two postop years since complications such as ingrowth are more frequent after two years.” The surgeons who prefer to perform surface ablation over the flap instead of lifting it say their approach is safer, but for different reasons. “When you ablate the flap,” says Chicago surgeon Jonathan Rosin, “there’s no possibility for flap-related complications such as epithelial ingrowth, torn flaps, et cetera.” Another surgeon agrees, saying, “It’s safer, with less risk of epithelial ingrowth, and it also permits the use of larger ablation patterns over older flaps.”

Phakic IOL Opinions

Twenty-three percent of the surgeons say they implant phakic lenses in their practices. Here are their thoughts on the pros and cons of phakic IOLs.

“They give good results and excellent vision,” says one surgeon. “Financially, though, they’re not as rewarding as LASIK. I reserve them for higher myopes.” Dr. Bernitsky uses the Visian ICL, but says, “I wish it came in quarter-diopter increments and that the cost were lower.” Another surgeon, though, says he likes the Visian ICL with the KS-AquaPORT because, “it’s easy to perform, has a fast recovery and is a one-step procedure.” Dr. Parkhurst says he appreciates phakic IOLs’ vision quality and removability. “I like the quality of vision with the Visian ICL procedure,” he says. “And the fact that the ICL is removable makes future cataract IOL calculations easier in comparison to patients who have had prior corneal refractive surgery. Also, phakic IOLs essentially induce no dry eye, which can be an issue with corneal refractive surgery in certain patients.”

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Pneumatic Retinopexy: Its History & Its Future

One of the pioneers of a still controversial procedure reminisces about its origins and looks at its role in current practice.

By Paul E. Tornambe, MD, FACS, Poway, Calif.

Although pneumatic retinopexy was first performed more than a century ago and resurrected in the 1930s, it was not refined and seriously brought to the attention of the retinal community until George Hilton and W. Sanderson Grizzard published their experience in 1986. D. A. Dominquez from Spain, Ingrid Kreissig from Germany and Harvey Lincoff from New York played major roles in modern-day pneumatic retinopexy. Dr. Lincoff was the first to report how an intravitreal gas bubble with proper positioning over a retinal break could result in complete resolution of subretinal fluid in his classic paper, using rapidly resorbing Xenon gas to locate a retina break. Had he placed a spot of cryopexy on the break (revealed as the gas bubble receded), pneumatic retinopexy would have been credited to him alone.

Early Days

I was chief resident at Pacific Medical Center in San Francisco at the time Dr. Grizzard did his fellowship with George Hilton across the bay in Oakland. I had the privilege of spending time with Dr. Hilton in the OR during that year. He always operated in the evening, after office hours, when things quieted down. He was very methodical; every detail was placed in a cubbyhole. “Paul, there are 13 causes of cystoid macular edema,” he would say, reciting them in the same order every time he gave “the sermon.” He also said there are 10 steps to retinal detachment surgery (scleral buckling), and he demonstrated how one step followed the other. He made retinal surgery appear very simple. He sparked my interest in retinal disease and helped me obtain a retina fellowship at Barnes Hospital in St. Louis with Ed Okun, MD. After I completed my retina fellowship, I hung my shingle in San Diego but kept in touch with Dr. Hilton, a mentor, and I frequently asked his advice in the early days of my practice.

The concept of pneumatic retinopexy came to light at an alumni meeting of the 1979 Paul Cibis Club shortly after my fellowship. Dr. Ed Boldrey, MD, gave a paper describing a bedside injection of air to salvage a failing scleral buckle (patients were admitted to the hospital in those days for scleral buckling). Dr. Boldrey’s talk was followed by the guest lecturer, Robert Machemer, MD, who made a very profound statement, “The retina wants to heal itself and if you don’t do too much to it, it probably will.” I recall sitting next to Dr. Okun and at the conclusion of Dr. Machemer’s talk, I turned to him and said, “Ed, why don’t we try the bubble first and if it doesn’t work, we can always insert the buckle.” He very politely told me I was nuts. I returned to San Diego and tried this technique.
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The following complications occurred 3 months after LASIK during the clinical trial: 0.0% (0/256) had corneal infiltrate or ulcer, 0.2% (1/488) had crystalline opacification or manifested keratitis, and 0.2% (1/488) had glaucoma.

**Contraindications**

The following complications did NOT occur 3 months following wavefront-guided LASIK during the clinical trial: 0.0% (0/844) had foreign body sensation, 0.0% (0/844) had pain, 0.0% (0/844) had photophobia, and 0.0% (0/844) had tearing.

**Adverse Events and Complications for Wavefront-guided Myopia**

Certain adverse events and complications occurred after the wavefront-guided LASIK surgery. No adverse event occurred during wavefront-guided treatments during this clinical study.

The following complications occurred 3 months after LASIK during the clinical trial: 0.0% (0/256) had corneal infiltrate or ulcer, 0.0% (0/256) had crystalline opacification or manifested keratitis, and 0.0% (0/256) had glaucoma.

**Adverse Events and Complications for Mixed Astigmatism**

 Certain adverse events and complications occurred after the wavefront-guided LASIK surgery. No predictive adverse events occurred during this clinical study. However, two events occurred which were considered related to treatment.

The following complications occurred 6 months after LASIK during the clinical trial: 0.0% (0/256) had corneal infiltrate or ulcer, 0.2% (1/488) had crystalline opacification or manifested keratitis, and 0.2% (1/488) had glaucoma.

The following complications occurred 6 months after LASIK during the clinical trial: 0.0% (0/256) had corneal infiltrate or ulcer, 0.2% (1/488) had crystalline opacification or manifested keratitis, and 0.2% (1/488) had glaucoma.

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on two patients with no insurance and no means of otherwise regaining their sight. Both cases worked! However, I was in practice just a few years and was not anxious to let anyone know just how far I deviated from the standard of care.

Howard Shatz, MD, started the West Coast Retina Study Club in the early 1980s and I attended a meeting in San Francisco where Dr. Hilton presented five cases of pneumatic retinopexy. I told him I had done two cases and asked where he got the idea. To my amazement he said he heard Ed Boldry’s talk at UCSF. At that meeting Neil Kelly said he also independently did a few cases.

Dr. Hilton subsequently presented his experience with 20 cases to the AAO and on the audiotape, which I cherish to this day, he magnanimously stated that Dr. Kelly in Sacramento and myself were also doing this procedure. We then put all our data together and published our experience in several papers.8-10 We subsequently shared our experience with others in an AAO instruction course consecutively for more than a decade (See Figures 1 & 2).

Dr. Hilton decided that the only way this new procedure would be accepted in the retinal community would be with a prospective, randomized, controlled clinical trial. He invited seven groups of fellowship-trained retina surgeons from across the country who had experience with pneumatic retinopexy and scleral buckling to participate in the trial. He outlined how pneumatic retinopexy would be performed, but told the participants to perform whatever scleral buckling operation they normally used. This trial could not be done today. We did not have IRB approval (I don’t think there was an IRB at that time); we used a gas that was not approved for intraocular use (the cost of the gas and lecture bottle was $14); and we funded the project internally, paying for the biostatistician who provided randomization envelopes. We did not charge the patient for the pneumatic operation. It was a very exciting time. Then, one day Dr. Hilton called me. He was a bishop in the Mormon Church and told me he had been called for a mission to Tahiti. He asked if I would take over the trial and, in a moment of weakness and complete ignorance what that meant, I said yes.

Dr. Grizzard and I subsequently put on a seminal meeting in San Diego. We invited anyone who was performing the operation to present his or her data, which we eventually published.11 All the presentations were similar, with about the same positive results and complications. We realized we were onto something good.

The Trial Begins

The Pneumatic Retinopexy Clinical Trial enrolled about 100 patients into the scleral buckle group and another 100 into the pneumatic retinopexy group. The process of randomization remarkably produced two very similar groups. After following the patients for six months, the data showed that pneumatic retinopexy reattached the retina almost at the same frequency as scleral buckling, but most importantly, quickly improved vision to the pre-detachment level more often than scleral buckling. It also showed that a failed pneumatic did not harm the eye. Writing the manuscript was quite challenging, for there was no Internet and no one was really using a computer. There were many revisions of the paper sent between San Diego and Tahiti (via DHL). Once the presentation was accepted by the AAO, I requested Dr. Lincoff to referee the paper. He was well-known as one who did not embrace the procedure, and I felt if he was positive about the paper, more surgeons might accept the operation. Dr. Lincoff did not disappoint; he was fair, pointed out all the weak points of the study, but also admitted there was some validity to the operation. After 18 more months of follow-up we presented the PR Clinical Trial two-year data, again at the AAO.
Pneumatic Retinopexy My Way, A Dozen Pearls

I once gave a lecture to a group of retina specialists from a very prestigious Northeastern university. One of the junior faculty members approached me at the end of the lecture and said, “My results are not as good as yours, but I don’t do the procedure exactly the way you do.” My technique is published in detail in the Transactions of the AOS. Here are some bullet pearls:

1. Most patients, if they meet the criteria, can undergo pneumatic retinopexy in the office exam chair. There are very few who cannot be gently and confidently talked through the operation. Don’t do the procedure in the middle of a busy office day. Bring the patient back at the end of the day for your relaxed and undivided attention.

2. If you can’t examine the entire retina well, don’t do the operation. A minor vitreous hemorrhage does not disqualify the eye. But if you have a small pupil, cataract or pseudophakic opacities that prevent you from seeing the periphery well, don’t do the operation.

3. Pseudophakia is absolutely not a contraindication to pneumatic retinopexy, assuming the intraocular lens is stable and the periphery can be examined.

4. Retrobulbar anesthesia is never needed. SubTenon’s xylocaine is all that is necessary.

5. Breaks at 12, 3 and 9 o’clock are easy to close. Breaks in the superior oblique meridians are harder to close. Inferior breaks are very hard to close but are possible in a limber, motivated patient. A positioning device such as the Escalon pneumo-level will greatly help with compliance.

6. If the break is not highly elevated, I do the procedure in one sitting with light cryopexy. I always use cryopexy, if possible, on breaks at 3 and 9 o’clock for if there is no pexy, the breaks tend to reopen on the trip back to the office for the first postop visit. If the break is so elevated that a large ice ball must grow from the probe to the break (liberating retinal pigment epithelial cells), I stage the operation and apply laser the next day. Beware that once the break flattens, it will be very difficult to find. Sometimes a laser spot (delivered with the laser indirect ophthalmoscope) can be applied to the ora to mark the meridian of the break. A careful drawing of the blood vessel network or an Optos wide-angle photo can be very helpful.

7. C3F8 is overkill. Ninety-five percent of detachments can be repaired with 0.5 to 0.6 ml 100% SF6. I use C3F8 only if the eye is large, or the break is large or extends over a few clock hours, or is posterior or inferior. I’m more concerned about not penetrating the anterior hyaloid and injecting into the space of Petit than I’m worried about fish eggs going under the retina. If a small amount of gas does get under the retina and a large bubble covers the tear, no rescue procedure is needed. Subretinal gas goes away faster than the vitreous bubble. If gas does enter the space of Petit, no treatment is needed; the bubble usually breaks through the next day.

8. I’m comfortable treating eyes with less than three clock hours of lattice. If there is lattice and/or there are several breaks, I consider 360 peripheral equator plus laser. These eyes have abnormal peripheral vitreoretinal adhesions and tend to form new breaks.

9. I always do a paracentesis before injecting gas with a #30 needle. If you pump up the eye with gas before doing a paracentesis, gas may enter the anterior chamber (even if phakic), and iris incarceration is more likely during the paracentesis.

10. I always use 5% povidone iodine; always use a speculum; always give 0.2 ml of subTenon’s gentamycin away from the injection and paracentesis site; and now always use a mask and almost never wear gloves.

11. I always examine the patient on the first postoperative day.

12. If the break is still open on day three, a rescue operation will likely be needed. If the break is closed and there is inferior subretinal fluid, no treatment is needed as long as the macula is attached. Sometimes subretinal fluid can linger for months. If the macula is off, there is likely an inferior break. The rescue operation should be performed by day five, especially if cryopexy was used. Pneumatic retinopexy gets a bad name usually because the eye is not rescued promptly. In the Pneumatic Retinopexy Clinical Trial, the incidence of proliferative vitreoretinopathy was the same for scleral buckle and pneumatic retinopexy. —PT

which showed that the operation was lasting and that almost 90 percent of patients with detachment of the macula regained reading vision.2,11

Pneumatic retinopexy has been controversial since the beginning and remains so today. Some surgeons were so concerned about the conclusions of the trial that they requested the raw data to personally review. Many published their poor initial experience with the procedure. Adverse events were quickly disseminated, several as single case reports.14-21 Rarely were the publications prospective or randomized.26 One trial reported the aggregate results of many surgeons, each contributing a few of their early attempts with pneumatic retinopexy with understandably poor results.2 Several papers concluded the operation was less successful in pseudophakic eyes, but also noted that failed cases ultimately did well.24,25

Today, many surgeons remain reluctant to treat the simplest detachment with pneumatic retinopexy when the eye is pseudophakic. We agree that the single operation success rate is not as high in pseudophakic eyes but the procedure still works well in most cases and, if it does fail, no harm is done. Dr. Hilton and I subsequently published a paper addressing these adverse experiences and showed how most complications are avoidable.20

Present Status & the Future

Pneumatic retinopexy is performed less often today for many reasons. More preoperative time is required to prepare and educate the patient; vitrectomy instrumentation is reliable; fewer fellows are adequately trained with scleral buckling; surgeons are economically punished for performing pneumatic retinopexy; and doctors are not responsible for the total cost of the intervention (including inevitable cataract surgery following vitrectomy).

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Figure 4. The best visual acuity is attained after a single pneumatic attempt. However, if the first pneumatic fails and is repaired with a second pneumatic operation, the visual results are still better than an eye attached with one scleral buckle. (Legend: PR = pneumatic retinopexy; SB = scleral buckle; SOS = single operation success; SOF = single operation failure.)

Pneumatic retinopexy will become more popular. Surgeons will be compensated by their outcomes and resources they consume. Even if one assumes a 60-percent pneumatic success rate, pneumatic retinopexy is still more cost-effective than buckling or vitrectomy.

One cannot separate the surgeon from the surgery. Pneumatic retinopexy requires a trained eye to find the breaks, and an experienced surgeon to select the right operation and perform the pneumatic procedure correctly, which appears deceptively simple on the surface. It is especially important to perform a recue operation in a timely fashion. I continue to perform pneumatic retinopexy because it remains the best way to restore pre-detachment vision (See Figure 4).

Finally, for a trip down memory lane I suggest you visit youtube.com, where you will find a short video of Dr. Hilton performing and narrating pneumatic retinopexy, by searching “George Hilton pneumatic retinopexy.”

Dr. Tom6amb6e is president of Retina Consultants, San Diego, and is the director of the San Diego Retina Research Foundation. He is past president of the American Society of Retina Specialists. He may be reached at 12630 Monte Vista Rd. #104, Poway, Calif. 92064. Phone (858) 451-1911, fax (858) 451-0566, or e-mail torr6ambpe@aol.com


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Femtosecond Laser in Anterior Segment Surgery

A specialist shares his thought process for evaluating the patient and choosing the steps to restore a smooth cornea.

By Roger Steinert, MD, Irvine, Calif.

Since the 1930s, physicians have been looking for ways to increase wound surface area and improve outcomes in penetrating keratoplasty. Unfortunately, the technical difficulty of the procedures kept these methods from becoming widely used. The introduction of the femtosecond laser has opened up new possibilities for transplant surgeons.

The Advantages

The laser uses near-infrared light to cut corneal tissue via photodisruption, which provides nonplanar cuts at a precise depth and pattern with minimal damage to surrounding tissue. The femtosecond laser cuts are consistent and reproducible, allowing for the creation of a variety of incision types using combinations of lamellar and vertical cuts. Additionally, the femtosecond laser has the ability to create straight cuts in complex shapes, such as decagonal and circular.

The “top-hat” was the first customized trephination pattern using the femtosecond laser. Studies have shown that this shape led to increased biomechanical wound stability with a sevenfold increase in resistance to leakage and possibly less astigmatism than traditional trephination PKP wounds.1,2 Today, corneal surgeons have a variety of trephination patterns to choose from, including the top-hat, mushroom, zigzag and Christmas tree shapes. All of these wound configurations create more surface area for healing and have better biomechanical strength than the traditional butt joint. The increased surface area of these incisions leads to improved tensile wound strength, which improves patient safety and allows for earlier suture removal, when indicated.

Factors preventing optimal outcomes in PKP include donor-host misalignment of the anterior surface; rotational misalignment and poor tissue distribution; excess and uneven suture tension; and slow and uneven wound healing. Using the femtosecond laser has allowed for certain improvements in these variable factors and has improved optical and mechanical outcomes.

Femtosecond laser-assisted PKP has demonstrated better natural alignment of the donor and host anterior surface, reducing one source of distortion. Additionally, improved sealing of the incision allows surgeons to use only enough suture tension to keep the incision apposed, which reduces distortion from the suture itself. Studies have also shown that femtosecond laser-assisted PKP provides rapid visual recovery and astigmatism amounts comparable to or slightly better than traditional blade trephination PKP.3-7

Patient Selection for PKP

Careful patient selection is the key to successful outcomes. Patients who have conditions that prevent proper laser applanation and suction are not...
good candidates for this procedure. Additionally, although the femtosecond laser has excellent cut penetration even through dense scars, severe peripheral corneal neovascularization may be a contraindication in certain cases. Small orbits or narrow palpebral fissures may not be able to accommodate the limbal suction ring required for laser use.

When choosing the graft size, consider the host corneal diameter (especially vertical), location of thinning or active corneal infection, and the presence of prior graft. In patients with ectasia, especially pellucid marginal degeneration, large or eccentric grafts may be needed. After the laser cut and before tissue removal, a posterior bridge of uncut tissue will maintain a closed eye and a formed anterior chamber. Therefore, accurate preoperative pachymetry is often crucial in cases where deep anterior lamellar keratoplasty is to be attempted, or, as is usually the case, in cases where the femtosecond laser is not located in the operating suite and corneal stability is required during the time between laser cut and corneal removal. Optical coherence tomography, Pentacam or ultrasound is used to check and program depth settings for the femtosecond laser incision.

Cutting the Graft and Surgery

The next step is graft cutting. The tissue is mounted on an anterior artificial chamber, and donor corneas are cut by the femtosecond laser using preprogrammed parameters set by the surgeon. Another option is to order the tissue from the eye bank precut with the same laser parameters as those to be used on the patient. The donor tissue diameter should be the same size as the host. The host laser cut can be performed under topical or retrobulbar anesthesia. However, more complex cutting patterns and alignment marks have increased the amount of time the suction ring remains on the eye, so many surgeons prefer using a preoperative retrobulbar block to ensure patient comfort.

Proper centration of the suction ring is the key to proper centration of the graft. The surgeon chooses a customized trephination pattern and programs it into the laser computer. The laser pattern always starts from the deepest part of the cornea and moves anteriorly. The IntraLase laser allows for a maximum diameter of 9 mm, with the ability to vary the side-cut angle from 30 degrees to 150 degrees.

As an example, with a zigzag incision, the laser parameters are a posterior side cut from deep stroma to anterior stroma at 30 degrees to the periphery and a second lamellar cut at a depth of 320 µm from the anterior surface. The second incision is intersected by the third incision, which is an anterior side cut that advances toward the anterior corneal surface at 30 degrees. The zigzag cut can have an anterior diameter of 8, 8.5 or 9 mm, based on the patient's corneal diameter and the surgeon's preference. Additionally, radial alignment marks are made on the host and donor corneas that facilitate precise suture placement and improved tissue distribution.

If the surgeon sees small bubbles from the eye bank of the foot pedal, and the laser will stop. As long as the laser has not reached Descemet's membrane, then the posterior depth can be reset, and the laser can be restarted within the posterior corneal stroma to maintain a bridge of uncut tissue.

If it is necessary to move the patient to the operating room after the laser corneal cut, globe stability can be ensured via a posterior bridge of uncut corneal tissue. Studies have shown that side-cut bridges are stronger than lamellar bridges. However, both types of bridges are stronger than full-thickness cuts. Posterior side-cut bridges are preferred over anterior side-cut bridges to minimize irregularities in the anterior contour and poor anterior graft-host fit. Additionally, posterior side-cut bridges offer the benefit of being easily extended with a blade into the anterior chamber without compromising the laser cut shape.

After the incision is made, the eye is treated with antibiotic drops and is shielded. Then, the patient is moved to the operating room. The host corneal button is separated with a blunt lamellar dissector to reveal lamellar and side-cut incisions made by the laser. Laser incisions usually separate cleanly; however, in some cases with dense corneal scarring, limited sharp dissection with a surgical blade or scissors may be needed. After blunt dissection, the blade enters the anterior chamber, and the corneal bridging tissue is cut with corneal scissors. The surgeon then sutures the donor cornea into place using his pattern of choice. Make sure to match the depth of the suture in the donor and host to ensure a lock and key fit.

Multiple studies have shown that endothelial cell loss, postoperative astigmatism and best spectacle-corrected visual acuity in femtosecond-laser assisted PKP are better than or equal to conventional PKP.

Figure 2. A zigzag incision being opened.
The top-hat and zigzag incision patterns are the most popular. One main advantage of femtosecond laser-assisted keratoplasty compared with traditional PKP is the accuracy of the fit between the donor and the host corneas. For this reason, the zigzag pattern may be the most biomechanically sound because it allows for consistent suture placement at approximately 50 percent depth, where the posterior side-cut and lamellar incisions intersect. In contrast, with the top-hat pattern, suture placement can vary, allowing the possibility of posterior wound gape. With the zigzag pattern, sutures are placed at the inner point of the Z, which provides good wound apposition at the deeper layers and anterior cornea.

At my institution, in a review of 173 eyes having undergone femtosecond laser keratoplasty, the average manifest astigmatism was less than or equal to 3 D, and average topographic astigmatism was less than or equal to 4 D as early three months postoperatively. This remained the case throughout the two-year follow-up period.

**Femto Lamellar Keratoplasty**

In addition to full-thickness keratoplasty, the femtosecond laser can be used for other forms of corneal transplantation, such as DALK, anterior lamellar keratoplasty (ALK), Descemet’s stripping endothelial keratoplasty (DSEK), and deep lamellar endothelial keratoplasty (DLEK).

Deep anterior lamellar keratoplasty with the “big-bubble” technique has been used successfully for multiple cases of stromal pathology with healthy endothelium, including infections, anterior stromal dystrophies, keratoconus and post-refractive ectasia. The DALK technique has been enhanced by the use of customized femtosecond trepanations, such as zigzag or mushroom patterns, by creating a posterior cut whose posterior depth lies within 50 µm to 100 µm of the endothelium, providing a guide for needle insertion and big-bubble dissection. If the dissection of Descemet’s membrane fails, surgeons can easily convert the procedure to a full-thickness transplant, which maintains the benefits of the femtosecond laser incision.

DALK for stromal corneal pathology and ectatic corneal disease provides many benefits, making it preferable to traditional PKP. Benefits include the safety of extraocular surgery, no risk of endothelial rejection due to preservation of the host endothelium, and a shorter postoperative course of topical corticosteroids. Although epithelial and stromal rejection is rare, surgeons still need to look for it.

Unfortunately, DALK with the zigzag pattern has a high failure rate of big bubble dissection. One solution is femtosecond laser pre-Descemet deep lamellar dissection. A smooth dissection is obtained by an ultralow energy multipass technique with the 150 kHz iFS IntraLase laser. The irregular ridges of previous deep corneal lamellar FS dissections are avoided.

ALK can be used for patients with relatively anterior pathology, including scars and anterior dystrophies. A sutureless technique using the femtosecond laser to create smooth lamellar dissections just inferior to the corneal pathology has been described.

DSEK allows surgeons to replace diseased host endothelium while retaining normal stroma and epithelium. The procedure offers decreased healing time, decreased astigmatism and a predictable change in corneal power.

Additional studies are under way to assess various energy and spot size patterns of the femtosecond laser and to use multiple passes to create a smoother donor bed.

Dr. Steinert is the Irving H. Leopold Professor and Chair of Ophthalmology, professor of biomedical engineering, and director of the Gatten Herbert Eye Institute at the University of California, Irvine.

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Nobel Therapeutics
And Ophthalmology

How the subject of Nobel-Prize-winning, landmark scientific research is making its way into our patients’ eyes.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and James McLaughlin, PhD, Andover, Mass.

The recently awarded Nobel Prize in chemistry recognized the contributions of two exceptional scientists, Robert Lefkowitz, MD, of Duke University and Brian Kobilka, MD, from Stanford University, for their work on the structure and function of g-protein coupled receptors, or GPCRs. This got us thinking about how important this family of signaling molecules is to ophthalmology, as they are to all areas of medicine. From Advair to Abilify, latanaprost to Lantasta, and Vicodin to Viagra, GPCR-targeted drugs have transformed therapy for countless conditions. This month we’ll consider the stuff from which scientific fame springs, taking a refresher course in g-protein signaling and a brief tour of some noteworthy GPCRs of the visual system.

Spotlight on G-proteins

The importance of g-proteins and the cell surface receptors that control their function is certainly reflected in the many scientists who’ve been honored by the Nobel committee. Julius Axelrod, Ulf von Euler, PhD, and Earl Sutherland, MD, won Nobel awards in the early 1970s for their studies of epinephrine and norepinephrine action, although many of these studies predate the concept of a g-protein. Alfred Gilman, PhD, and Martin Rodbell, PhD, shared the 1994 Nobel Prize for research which established the fundamentals of g-protein signaling, and Richard Axel, MD, and Linda Buck, PhD, were awarded the 2004 Prize for their work on g-proteins in the olfactory system. This level of attention from the Nobel committee is not surprising given that the gene family encoding GPCRs represents 1 percent of the human genome. The therapeutic impact may be even more impressive: It’s been estimated that as many as half of all currently marketed drugs target some aspect of GPCR-based signaling pathways.

Drs. Lefkowitz and Kobilka’s research provides a clear, conceptual understanding of how hormones, neurotransmitters and drugs interact with these receptors and how those interactions lead to a remarkable diversity of responses seen throughout the body. As a fellow in Dr. Lefkowitz’s lab in the late 1980s, Dr. Kobilka was an integral part of the team that first cloned adrenergic receptors and showed they were close relatives to rhodopsin. Since then, assembling and defining the many other participants in GPCR signaling has proceeded at a continually accelerating pace. While the Lefkowitz lab has focused on the intricate details of GPCR function, Dr. Kobilka’s laboratory took on the herculean task of crystallizing purified samples of receptor protein. Protein crystals can be used to generate high-resolution structures which can provide a 3-D explanation for decades of biochemical studies. Using the analogy of the lock and key, most historical drug design has involved random testing to find keys that fit the lock of their target. The pairing of refined functional studies and crystallography of GPCRs, however, provides us with a dynamic model of the lock, and the opportunity to “cut keys” in a whole new way.

The Layers of GPCR Signaling

The function of any receptor is to detect chemical or physical messages in the extracellular world and...
translate those incoming messages into a coherent cellular response. GPCRs are positioned to do this as trans-membrane proteins, with one face exposed on the surface and another on the inside of the cell. The receptors cycle between three states that depend upon presence of an extracellular message, as depicted in Figure 1. That message can be a neurotransmitter, a hormone, a divalent ion or a photon.

In the resting state, the GPCR is associated with another cycling protein complex, the g-protein, which is formed by three subunits (an $\alpha$, a $\beta$ and a $\gamma$; a heterotrimer) bound together at the intracellular surface of the GPCR. The $\alpha$ subunit has a guanine nucleotide binding site (thus the name g-protein), occupied by guanosine diphosphate. When compounds such adrenaline or histamine bind to the extracellular face of the GPCR, changes in the protein shape promote the dissociation of GDP and subsequent guanosine triphosphate binding to the g-protein inside the cell. Binding of GTP frees the $\alpha$-protein from the activated state GPCR, and it separates into $\alpha$ and $\beta\gamma$ components that can then move through the cell to activate target enzymes, ion fluxes and genes. The activated GPCR can be transitioned through a desensitized state by phosphorylation at one or more intracellular sites; this slows the transition back to the resting g-protein bound state, or may lead to association with proteins called arrestins, which can signal another set of cellular responses to GPCR activation.

Although there are hundreds of different GPCRs, each typically couples with one of a dozen or so $\alpha$ subunits: thus, the beta adrenergic receptors commonly signal via an $\alpha\beta\gamma$ g-protein, while the histamine H1 receptor couples to $\alpha\beta\gamma$ heterotrimer. Each of these $\alpha$ subunits elicits a characteristic cellular response that may include modulation of adenylate cyclases, guanylate cyclases, or phospholipases. In addition, the $\beta\gamma$ dimer also participates in signaling in some cells by modulating the activity of membrane ion channels.

GPCR signaling can also be targeted by a receptor-independent g-protein modulation, and these are increasingly being recognized as physiological regulators of GPCR signaling. The best examples are the RGS proteins (regulators of g-protein signaling) that function to stimulate the GDP-GTP turnover independent of GPCR activation. Evidence for such proteins comes from many studies, including analysis of the GTPase activity of transducin, the heterotrimeric g-protein that partners with rhodopsin. Purified transducin hydrolyzes GTP to GDP with a $t_{1/2}$ of about 15 seconds, but the rate of retinal deactivation has a $t_{1/2}$ of about 0.5 sec. The human retinal RGS responsible for this effect is now designated RGS9, one of about two dozen such regulatory factors. It seems that all g-proteins have an intrinsic rate of GDP-GTP turnover, and the activation of GPCRs by ligands (or drugs) enhances that rate to trigger g-protein signaling. Overlaying this pathway are the RGS proteins, which act by further enhancement of GDP-GTP turnover. Of the 20 or so identified RGS proteins, most are specific for a single...
α subunit. Their role in modulating muscle contractility and maturation is well-established, and recent work suggests an important function in the immune system. There are also examples of RGS proteins in the visual system, and the interest in their functional importance and potential therapeutic targeting is likely to expand in the future.

**GPCRs in the Eye**

The majority of drugs used by practicing ophthalmologists, particularly those used to modulate autonomic function, act at GPCRs. The adrenergic receptors of the ciliary epithelium provide a clear example of how different g-protein α subunits and different GPCRs can orchestrate homeostatic control. Beta adrenergic GPCRs in the ciliary epithelium couple to a heteromeric g-protein with an α subunit; activation of this receptor by epinephrine or other beta agonists leads to an increase in cellular cyclic AMP, which stimulates the secretion of aqueous humor. These same tissues also express alpha adrenergic receptors that couple to an α subunit. The activation of this pathway causes an inhibition of cAMP synthesis and a reduction in aqueous humor. The net output will depend on the relative amounts of epinephrine and norepinephrine in the extracellular environment and their integration over time. Of course, both of these pathways are exploited in therapies for primary open-angle glaucoma, with beta antagonists such as timolol and alpha-2 agonists like brimonidine acting to suppress aqueous humor formation.

One ocular tissue where RGS proteins may impact GPCR function is the mast cells of the conjunctiva that undergo allergic conjunctivitis. Typically, mast cells are stimulated to release histamine via binding of surface IgE-antigen complexes, but degranulation can also be stimulated or potentiated by activation of GPCRs for adenosine (the A3 isoform) or chemokines such as CXCL12. These receptor pathways can also stimulate release of other vasoactive mediators such as IL-8, and they are regulated by RGS13. Surprisingly, RGS13 appears to have a function independent of its effect on GDP-GTP turnover, and over-expression of RGS13 in mast cells inhibits IgE-mediated degranulation, but this effect doesn’t appear to be mediated via a heteromeric g-protein. Consistent with these findings, RGS13 knockout mice are hyper-responsive to IgE degranulation and more susceptible to anaphylaxis. Thus, RGS stabilizers or surrogates may find a use in treatment of allergic disease.

The classic example of a GPCR in the eye is rhodopsin, the visual receptor that responds to photons of light in much the same way as an adrenergic receptor does to epinephrine. The g-protein coupled to rhodopsin is called transducin, and it acts by shutting off a membrane current when it’s in the active, GTP-bound phase of the cycle. Once the GTP is hydrolyzed, the transducin is deactivated, and the current is reactivated. This turns out to be a critical step in photo-accommodation, the process of visual adaptation when going from an area of bright light to darkness (or vice versa). For most people, this requires a few seconds to complete.

At the cellular level, photo-accommodation depends upon a retinal G protein, RGS9, that regulates the speed of transducin GDP-GTP turnover. In the past decade, researchers have identified a number of patients with bradyopsia, or slow vision, who require many minutes to adapt to changes in light intensity. In each case, this condition has been traced to mutations in either RGS9 or a related protein, R9AP, that acts to stabilize RGS9 in retinal cells. While this research was the first example of a human disorder linked to an RGS defect, it is not likely to be the last.

**Future GPCR Discovery**

The work of Drs. Leftkowitz and Kobilka (and others) has revealed the stunning complexity of GPCR signaling, and demonstrated a seemingly inexhaustible supply of opportunities for therapeutic intervention. Beyond simply targeting a molecule or a pair of interacting proteins for high-throughput-based approaches, we begin to more fully understand how we want our drugs of the future to interface with specific GPCR signaling pathways. For example, Dr. Leftkowitz’s lab has identified and characterized a family of GPCR-interacting proteins, the arrestins, that were initially thought to be part of the cell’s GPCR desensitization/recycling system. It turns out they do much more than that: Internalized GPCR-arrestin complexes bind with other cellular partners and activate a number of signal pathways, including the ERK/MAP pathway. Perhaps more interesting from a therapeutic perspective is that the degree to which arrestin pathways are activated is ligand-dependent, and may represent an underlying explanation for side effects associated with some GPCR targeted drugs. While this field is very young, it’s thought that developing new ligands with a defined bias for activation of this second GPCR signaling pathway could find many therapeutic applications.

Pharmacologists love the idea of rational drug design but, unfortunately, as with many quests, unfortunately the structural resolution of multiple GPCRs alone hasn’t brought us to the end of the drug development rainbow. The power of Dr. Kobilka’s structures is that he has...
paired them with functional studies that allow us to visualize the protein as it proceeds from resting to activated states. This is why their work is so important: Watching the movements of a complex protein such as a GPCR on an atomic scale will allow for dynamic modeling of drug binding sites and the transitions they undergo. Ultimately, knowledge that we gain from these observations will help us choose any phase of the GPCR activation pathway as a drug target. The therapeutic potential of such a choice seems eminently worthy of a Nobel Prize.

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School and senior clinical scientist at the Schepens Eye Research Institute. Dr. McLaughlin is a medical writer at Ora Inc., in Andover.

Dear Residency Directors,

We would like to invite you to review this Save the Date Calendar for third-year residency programs we are planning for 2013. Each program offers a unique educational opportunity for third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide residents with a state-of-the-art didactic and wet lab experience. The programs also serve as an opportunity to network with residents from other programs. After reviewing the material, it is our hope that you will select and encourage your residents to attend these educational programs.

Best regards,

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OCT and Glaucoma: Artifact Alert

As more glaucoma specialists rely on this technology, being aware of its limitations has become increasingly important.

Sanjay G. Asrani, MD, Durham, N.C.

Our ability to help our patients often depends on technology, and one of the most useful technologies to come along in recent years is optical coherence tomography. OCT is now very commonly used by both ophthalmologists and optometrists as a means to have additional documentation of the nerve fiber layer status. Some doctors are using it to measure macular thickness and assess the status of glaucomatous damage. It can help us confirm that the visual field defect we found is not an artifact, or conversely, reveal that the structure is undamaged, so the visual field abnormality is an artifact. Sometimes OCT findings also help to reassure the patient by showing him concrete evidence that the extent of the loss is very small, or perhaps very extensive, which might make him more inclined to accept more aggressive therapy.

In the past, many doctors used instruments such as the GDx and HRT for this purpose, but today the vast majority rely on OCT instead, for several reasons. For one thing, OCT data is cross-sectional and not interpolated. The HRT uses certain floor and ceiling patterns to extrapolate the thickness of the optic nerve rim and related data; the GDx generates data by measuring polarization. In contrast, OCT gives you the actual thickness of the tissue—a real structural measure. Secondly, OCT can give you information about multiple structures, including the nerve fiber layer, optic nerve head and macula. In contrast, the GDx can only give you information about the nerve fiber layer and the HRT can only give you information about the optic nerve head.

The end result is that doctors are now making decisions about whether or not to treat—and how aggressively to treat—based on information provided by OCT instruments. But as our reliance on this technology increases, so does the cost of missing errors or overlooking shortcomings inherent in the technology. That makes it crucial for doctors to understand that OCT instruments have potential pitfalls. If we aren’t educated about these issues, we’re going to be led astray, to the detriment of our patients.

Red & Green Disease

I’m seeing the consequences of this type of error more and more frequently. People are referred to me for glaucoma diagnosis when there is absolutely no glaucoma, simply because an OCT scan was
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abnormal. And I’m seeing patients who have glaucoma but were told they did not have any disease because their OCT results appeared to be normal. In both situations the doctor failed to realize that artifacts were affecting what the instrument showed.

When doctors are misled by false negatives or positives on OCT, we call it “red disease” or “green disease.” Red and green are colors used by the OCT machines to identify abnormal and normal; yellow is borderline. Red disease is when the OCT mistakenly indicates that something is abnormal; green disease is when the OCT data shows no sign of abnormality, but the eye is, in fact, in trouble. Many clinicians take OCT results at face value, so seeing red automatically gives them pause, while green reflexively encourages them to proceed, reassuring them that everything is normal.

In fact, there are many things that can lead to erroneous results from these instruments. For starters, these are average assessments made by the computer software, and they’re based on normative databases. Normative databases are not exhaustive; they’re usually based on 300 to 500 patients. The patients in the normative database do not necessarily include high myopes, high hyperopes, children or members of different races.

The most common OCT problem, in terms of comparison to normative databases, comes from refractive extremes, especially high myopia. High myopes’ measurements tend to fall outside of the normal range, showing up as red. On the other hand, small focal areas of damage in any eye often show up as green because the instrument averages the thickness in a particular sector. The average is often within the normal range, despite the focal loss. So the whole printout is green, giving the impression that there is no damage present.

Unless there’s a concerted effort to train people to take artifacts into consideration when interpreting the data from these instruments, we’re going to have a lot of patients being treated unnecessarily—and a lot of patients who don’t get treated when they should be.

Types of Artifacts

The artifacts that we’ve encountered most often fall into these categories:

- Acquisition-dependent artifacts. These are caused by the person who is acquiring the images. The operator, for example, may not place the ring measurement of the nerve fiber layer concentric with the optic nerve. If the ring is placed eccentrically, so that it cuts across the edge of the optic nerve, then the measurement will not read as normal. The way to avoid this problem is to have the doctor look at the raw images to make sure that the data collected is good enough to produce accurate results. The difficulty is that doctors have a limited amount of time; they can only look at so much data per patient in the clinic. However, a false report is even more time-consuming in the long run, so this really does need to be added to the doctor’s responsibilities. The doctor should look at the raw data in front of the patient, on the computer screen, as a matter of course. He can make sure it’s correctly acquired, instead of simply accepting it at face value.

- Disease-related artifacts. Sometimes the disease itself can
fool the machine. The simplest example is that high myopes often have peripapillary atrophy, which may cause the software to fail to identify the nerve fiber layer in those regions.

Another common pathology-related artifact is epiretinal membranes. Although epiretinal membranes can occur in any patient, their presence is not easy to rule out because they’re just a slightly brighter layer on top of the retina. What often reveals them is the fact that they tend to be wrinkled. For that reason, if you see that the top retinal layer is wrinkled, you should assume an epiretinal membrane is present. (Of course, in some cases you may simply see what looks like a double edge to the nerve fiber layer.)

It’s also important to be sure that the software has correctly identified the upper and lower boundaries of the layer it’s scanning, because in some situations the software has trouble finding the boundaries. For example, sometimes the posterior vitreous surface that’s just above the retina will be mistakenly identified as the upper edge of the retina. You have to look at the raw data to identify where the software is placing the boundaries.

- **Instrument-related artifacts.** The two most common problems here are patient head tilt and microsaccades. Some instruments correct for these concerns, but others don’t. The former is an issue because a patient may put his head in one position during a scan and then put his head in a slightly different position at the next visit. Unfortunately, even an 8-degree tilt results in a major difference in the thickness reading. The only certain way to avoid this problem is to own a machine that’s designed to compensate for this. Likewise, the problem of microsaccades is avoidable if the OCT instrument has eye tracking and can confirm that the eye was being tracked during the measurements. Many of the recent instruments come with this feature, but some of the earlier models did not. Images with artifacts due to microsaccades have areas that appear “blacked out,” which can be identified on the printout. Also, the image quality numbers can alert you to a poor quality scan.

### Managing the Problem

Despite these caveats, if you’re able to identify and compensate for the artifacts that can distort the data, OCT is a very robust technology. It can be used to not only diagnose very early glaucoma, but also to monitor progression. The artifacts can have
a serious impact, but there aren’t too many of them, so it is possible to manage them. (Incidentally, very few people are using time-domain OCT—the earlier version of this technology—any more, but the same principles apply. Time domain doesn’t produce as many images, or images with as much detail, so you can be led astray even more because you’re working with less information.)

The issue is that we do have to manage this problem; we can’t just accept the data an OCT instrument gives us. We have to be willing to invest our time to look at the raw images and see how the software has analyzed it. This adds to the doctor’s burden, but powerful technology comes with responsibility. If we’re going to be able to use OCT to help us manage glaucoma, we’ll have to spend the time to make sure that what we’re getting from the machine hasn’t been altered by artifacts.

One way to manage this issue is to train technicians to check for these artifacts. We’ve done that in our office. When our technicians detect an artifact, they go to the source of the artifact and print out the extra images that are needed to identify it. They flag it “artifacts noted.” This doesn’t relieve the doctor of responsibility, but it certainly saves us time and increases the odds that false readings will be caught and corrected. (Of course, before technicians can be trained to look for these artifacts, the doctor has to recognize that this is an issue. Many doctors still are not aware that OCT artifacts are misleading them.)

As for what the future holds, these instruments are evolving as we speak. I expect that soon the instruments will identify pitfalls for us; flags will say, “Layer not identifiable” or “Note vitreous boundary.” They may not identify the pathology or the actual artifact, but they will tell us that something is wrong. I think we’ll see something along these lines soon.

**Spreading the Word**

OCT is a real, solid advance in glaucoma management. I can’t do my job without it. But if we want to have a major advance in technology in our armamentarium, we’re going to have to be aware of it’s shortcomings and compensate for them. To that end, education is the key. The more doctors realize that there’s a problem and learn to avoid it, the better. REVIEW

Dr. Asrani is professor of ophthalmology at the Duke Eye Center in Durham, N.C.

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Despite advances in various technologies, LASIK monovision remains the most popular option for eligible presbyopes. Surgeons say the key word is “eligible,” and stress that it’s important to select the right patients who are ready and willing to adapt to a new way of seeing the world. Here, several experienced refractive surgeons share their tips on how they evaluate patients’ eligibility for monovision, and take a look at what might be the next generation of monovision treatment.

Passing the Test

Surgeons say they take care in evaluating patients for monovision in order to increase the likelihood of success.

“If patients have used monovision with contact lenses, they’re usually great candidates,” says Deepinder Dhaliwal, MD, director of the cornea and refractive surgery service at the University of Pittsburgh Medical Center. “As presbyopes, it also depends on how particular they are about their vision. If it’s someone who doesn’t do a lot of close work, just reads casually, that type of thing, I think that’s a great candidate.” Dr. Dhaliwal prefers a monovision trial in the phoropter to a contact lens trial in most cases. “If they’re looking at the chart binocularly and don’t notice the blur in one eye, I think they’ll do very well, typically,” she says. “So I don’t always do a contact lens trial for every monovision candidate, because the nice thing is, if they end up hating monovision, I can always enhance them.”

Though surgeons differ a little on how they decide how much anisometropia to create with the monovision, they all agree that -1.5 D is probably the upper limit. “The amount of monovision I create is partly based on age,” says Ronald Krueger, MD, director of refractive surgery at the Cleveland Clinic. “If the patient is in his very early 40s, I’d do what I call half monovision, something like -0.75 or -1 D. If they’re in their later 40s or in their 50s, I’d do closer to -1.5 D. The -1.5 D level is about a focus of two feet, which is enough to give them enough mid-range vision to be comfortable and enough reading to get by.”

Monovision also involves a lot of chair time where the patient is made to understand the effects of the procedure. “One of the big things about success with monovision is that it requires a discussion with the patient about the fact that it’s not a static process,” says Edward Manche, MD, director of cornea and refractive surgery at Stanford University’s Eye Laser Center. “It’s a dynamic process that changes over one’s life. In their 50s, at -1.5 D of monovision, they’ll lose the near vision but preserve the intermediate and distance. So, for example, reading a menu in dim light will become increasingly difficult.”

There are also certain patients who may be predisposed toward not being successful with monovision. “I think the worst candidate is someone in his early 40s with low myopia, who is used to taking off his glasses to read,” says Dr. Manche. “The other ones with whom I haven’t had great success are emmetropic presbyopes. They’re used to excellent distance acuity in both eyes and to try to take one of their eyes and make it see well for near, I’ve had poor success with that, personally.”

Laser Blended Vision

Professor Dan Reinstein, MD,
Dan Reinstein, MD, FRCSC, of the London Vision Clinic in the United Kingdom, developed a new approach which modifies monovision laser vision correction and was implemented by Carl Zeiss Meditec as a software upgrade called Presbyond Laser Blended Vision for the MEL 80 excimer. One of the laser blended vision’s main goals is to create a blend zone of vision between the patient’s eyes at intermediate focal distances.

“The challenge in treating presbyopia is to achieve good binocular vision at far, intermediate and near distances while also maintaining optical quality,” says Dr. Reinstein. “The well-established principles of contact lens monovision have been used in laser refractive surgery, but many of the limitations of contact lens monovision also affected laser refractive surgery-induced monovision. These limitations include loss of fusion due to anisometropia, poor intermediate vision, poor distance vision in the near eye, reduced binocular contrast sensitivity, and reduced—or even broken—stereoacuity.

“Therefore, with Laser Blended Vision we incorporated another natural visual process—filtering of spherical aberration—to increase the depth of field in each eye and achieve good binocular vision at all distances,” Dr. Reinstein continues. “Introducing some spherical aberration disseminates the retinal focal point, meaning that there is a wider range of distances where the focus is equivalent, although slightly reduced, but the perceived image is still sharp due to the natural ability of the visual cortex to ‘process’ spherical aberration. This range is the depth of field and can be demonstrated by the better-than-expected distance vision in the near eye; the mean visual acuity is about 20/45 whereas 20/80 would be expected for -1.50 D.” He says that when this increased depth of field is combined with a micro-monovision (i.e., relatively lower degree of anisometropia), good near vision can be achieved with a functional level of uncorrected stereoacuity—provided that the patient has binocular function. Dr. Reinstein notes that too much SA, however, results in the visual cortex no longer being able to process it, resulting in quality of vision symptoms.

The typical candidate for Presbyond LBV is anyone who would be eligible for LASIK with the Carl Zeiss Meditec MEL 80 excimer and who passes the +1.5 D test.

For the LBV procedure itself, Dr. Reinstein considers a number of factors, including the patient’s age, accommodative amplitude, preoperative wavefront, tolerance of anisometropia and the amount of refractive error. “The software then combines these factors to generate an ablation profile with the aim of leaving the patient with an appropriate level of spherical aberration in order to maximize the depth of field without compromising contrast sensitivity, stereoacuity or night vision.”

In a study Dr. Reinstein performed using LBV, at one year, he reported that binocular uncorrected distance vision was 20/20 or better and uncorrected near vision was J2 or better in 95 percent of 136 myopic patients (≤ -8.50 D), 77 percent of 111 hyperopic patients (≤ +5.75 D), and 95 percent of 148 emmetropic patients (within ±0.88 D). “The safety was the same as for standard LASIK, with no eyes losing more than one line of CDVA and contrast sensitivity was either the same or slightly better than preop,” he says.

Dr. Reinstein says the procedure works because it is based on the way our brain interprets retinal images. Says he, “The key to this approach was to base it on the natural mechanisms of spherical aberration processing and binocular fusion.”
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Antibiotics Relieve Symptoms of MGD

A prospective, observational, open-label study from Kentucky suggests that the signs and symptoms of meibomian gland dysfunction, as well as spectroscopic characteristics of the meibomian gland lipids, improve after therapy with topical azithromycin ophthalmic solution and oral doxycycline treatment. However, the mechanism of action of doxycycline may be different from that of azithromycin.

Signs of MGD were evaluated with a slit lamp in subjects with symptomatic MGD and symptoms were measured by questionnaire. Meibum lipid-lipid interaction strength, conformation and phase transition parameters, and meibum protein content, were measured using Fourier transform infrared spectroscopy and principal component analysis. Terpenoids, short-chain CH3 moieties, lipid oxidation, wax, cholesterylesters and glycerides were measured with a proton nuclear magnetic resonance (1H-NMR) spectrometer.

Topical therapy with azithromycin and oral therapy with doxycycline relieved signs and symptoms and restored the lipid properties of the meibomian gland secretion towards normal. Compared with four weeks of azithromycin treatment reported in a previous study, oral doxycycline treatment was slightly less effective in improving foreign body sensation and the signs of plugging and secretion. In subjects with clinical evidence of MGD, changes in ordering of the lipids and phase transition temperature were brought closer to normal with azithromycin treatment than doxycycline treatment. Treatment with doxycycline but not azithromycin restored the Fourier transform infrared spectroscopy-principal component analysis scores and relative area of the 1H-NMR resonance at 1.26 ppm. Both doxycycline and azithromycin treatment restored the levels of the relative areas of the 1H-NMR resonance at 5.2 and 7.9 ppm to normal levels. The levels of meibum protein and meibum lipid oxidation were not influenced by azithromycin or doxycycline treatment.

Sensitivity and Specificity of AdenoPlus Test

U.S. researchers have determined that the AdenoPlus test is both sensitive and specific at detecting adeno viral conjunctivitis. Of the 128 patients presenting with a clinical diagnosis of acute viral conjunctivitis, of the 128 patients presenting with a clinical diagnosis of acute viral conjunctivitis who were enrolled in this prospective, sequential, masked and multicenter trial, the tear fluid of 36 patients was found to be positive for adenovirus either by viral cell culture with confirmatory immunofluorescence assay or polymerase chain reaction, while 29 patients results were found to be positive by both CC-IFA and PCR. When compared only with CC-IFA, AdenoPlus showed a sensitivity of 90 percent (28/31) and specificity of 96 percent (93/97). When compared only with PCR, AdenoPlus showed a sensitivity of 85 percent (29/34) and a specificity of 98 percent (89/91). When compared with both CC-IFA and PCR, AdenoPlus showed a sensitivity of 93 percent (27/29) and a specificity of 98 percent (88/90). When compared with PCR, CC-IFA showed a sensitivity of 85 percent (29/34) and specificity of 99 percent (90/91).

Glaucoma Control with Drainage Device and PK

Doctors from the University of Florida College of Medicine performed a review of records of all patients at their institution who underwent both a glaucoma drainage device placement and penetrating keratoplasty from January 1, 1998 to December 31, 2003, and determined that GDD placement can provide glaucoma control in a high percentage (71 percent) of eyes with PK, even at five years. Glaucoma outcome was assessed by postoperative intraocular pressure, number of glaucoma medications and need for further glaucoma surgery.
while corneal grafts were assessed for clarity. Twenty-eight eyes of 27 patients were studied. All eyes had GDD placement in the anterior chamber. The mean pre-GDD IOP was 28.8 ±10.3 mmHg on a mean of 2.6 ±0.8 glaucoma medications. At five-year follow-up, the mean IOP was 13.0 ±5.9 mmHg on a mean of 0.9 ±1.0 medications. GDD implantation successfully controlled glaucoma in 96 percent at one year, 96 at two years, 79 at three, 75 at four and 71 percent at five years. Grafts remained clear in 96 percent at one year, 82 at two years, 75 at three, 57 at four and 54 percent at five years. The success of PK in GCD remains reasonable (54 percent) at five years. IOP control and graft survival rates are comparable with earlier published studies with shorter follow-up or tube placement in the vitreous cavity. Failure of glaucoma outcome or graft survival was associated with prior intraocular surgeries.

J Glaucoma 2012;21:608-614

Decreased Postop Endophthalmitis Rates After Institution of Intracameral Antibiotics

Physicians at Kaiser Permanente in the Diablo Service Area in California performed a time-trend study on increasing adoption of intracameral injections after phacoemulsification cataract surgery, and concluded that the adoption coincided with a decline in the rate of postoperative endophthalmitis.

Three time periods were identified for this study: 2007; 2008 to 2009; and 2010 to 2011. In 2007, patients primarily received postop antibiotic drops without intracameral injection. During 2008 and 2009, patients received intracameral cefuroxime unless contraindicated by allergy or posterior capsule rupture and the surgeons’ usual postop topical drop regimen. During 2010 and 2011, all patients received an intracameral injection of cefuroxime, moxifloxacin or vancomycin while topical antibiotics were used according to surgeon preferences. The rates of postop endophthalmitis during these three periods were calculated; 19 cases of endophthalmitis occurred in 16,264 cataract surgeries. The respective rates per 1,000 during the three time periods (2007; 2008 to 2009; 2010 to 2011) were as follows: 3.13 (95 percent CI, 1.43-5.93); 1.43 (95 percent CI, 0.66-2.72); 0.14 (95 percent CI, 0-0.78).

Evaluated separately were consecutive patients without PCR from a subgroup of three surgeons who used intracameral injection alone without preop topical antibiotics; a low infection rate was observed with injection alone, with only one case of endophthalmitis observed in 2,038 patients (rate per 1,000: 0.49; 95 percent CI, 0.01-2.73).

J Cataract Refract Surg 2013;39:8-14
Shishtila N, Wertheim K, Herrinton L.

(Continued from page 34)

refractive data, updated multiple times per second; a high-resolution image of the eye providing the movie of the surgery as it occurs; and an intuitive, qualitative refractive graphical display laid over the video of the surgery. “With this information, the surgeon can, for example, see the change in astigmatism as he or she does a limbal relaxing incision, or dial a toric IOL into place,” says Dr. Linder. “HOLOS effectively becomes a guidance system toward achieving the refractive goal.”

In terms of availability of the device, it’s possible that U.S. surgeons will have a commercial model some time this year. “Clarity Medical Systems’ current plan is to have HOLOS IntraOp ready for limited release in the United States by the end of 2013,” Dr. Linder says.

Another potential system for intraoperative aberrometry is the Aston Aberrometer, which is in the prototype testing phase at Solihull Hospital and Aston University in Birmingham, United Kingdom. The system uses the Hartmann-Shack principle to return measurements in real time, and its designers say it’s designed to be attached to a slit lamp or under the surgical microscope coaxial with the surgeon’s line of sight.

Uday Bhatt, MD, an ophthalmologist taking part in the device’s development, says it has a dioptic range of around 45 D, and can measure aberrations up to the sixth order. “Measurement depends on which part of the reading you want to focus on—higher or lower,” he says.

“The lower order will give you the refraction and spherical aberration as well as toricity. We haven’t done much work on the toric as of yet. At some point, though, we will go through the study protocol to perform a study of its use with toric lenses, as well.”

In a recent study of the device, Dr. Bhatt and his colleagues attached the aberrometer to a modified slit lamp base and used it to record refractive error and higher-order aberrations in 75 subjects. They compared the findings to those from an existing aberrometer, the Topcon KR1W. In a proof of concept, they found the Aston’s measurements to be similar to the Topcon’s.

The next step is to look into intraoperative use. “Right now, we’re looking at whether we can actually use it intraoperatively and measure the refractive error of the aphakic eye,” says Dr. Bhatt. “That’s the potential we feel it has.”

Drs. Weinstock and Stephenson are consultants to WaveTec. Dr. Chang is a consultant to Clarity Medical Systems.

Reichert Technologies’ new Reflex Ultrasound Bio-Microscope safely images the anterior and posterior segments of the eye, delivering a superior view not available through other exam methods. Reichert’s next-generation UBM now offers a larger viewing area, a user-friendly, touchscreen interface and software improvements, the company says.

The compact unit is ideal for practices treating glaucoma patients, as well as for cataract and cornea specialists, providing valuable information for the treatment of phacomorphic lenses, plateau iris syndrome, cysts, tumors, retinal tears, cells in the vitreous chamber and vitreous hemorrhages.

The convenient test can be performed within five minutes by a technician or doctor. A ClearScan disposable probe cover ensures that the UBM’s probe will never make contact with the eye. Patients can remain upright in an exam chair throughout the procedure, with no need for a water bath or scleral shell.

Procedures using the UBM are billable through a well-established Medicare code.

The device is approximately the same size as a computer monitor, requiring very little space in an exam room.

Images captured on Reichert’s Reflex UBM are DICOM-compliant and can be exported to electronic medical records. The device also has a USB port and offers Ethernet connectivity. For information, visit reichert.com.

Reliance Launches Xoma Exam Lane System

Reliance Medical Products is now taking orders for its Xoma system, the first fully automated exam chair and instrument stand that incorporates programmable lighting, slit lamps, automated refraction control and imaging devices into one unit. Built-in tablet technology provides instant access to patient screening tests, acuity testing, images and educational videos.

Xoma’s ergonomic design was created with doctor comfort as a top priority, while offering practices a solution that optimizes space in the exam room. The system also is handicap-accessible.

Xoma incorporates programmable lighting that will automatically dim the room lights when the slit lamp is in use and return the lights to full brilliance when the exam is complete. The tablet integrated into Xoma eliminates the need for separate near-point cards and color test books.

The flat-panel screen also can display educational, advertising or entertainment content, possibly increasing patient satisfaction with the treatment and service received. The screen can play videos and slide shows to promote products, procedures, services and referral programs that help increase revenue.

Images and other patient data can be accessed from the patient record through electronic medical records. The devices and software incorporated into Xoma can be easily upgraded as new innovations are developed. The system operates on an open platform, making it functional well into the future.

Orders for the Xoma System can be placed by making a reservation online at ecoxoma.com, or by phone at (513) 336-7255. The company expects to begin delivering the system during 2013. REVIEW
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**RESTATIS®**
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**INDICATIONS AND USAGE**
RESTATIS® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical antiinflammatory drugs or using punctal plugs.

**CONTRAINDICATIONS**
RESTATIS® is contraindicated in patients with active ocular infections and in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

**WARNING**
RESTATIS® ophthalmic emulsion has not been studied in patients with a history of herpes keratitis.

**PRECAUTIONS**
General: For ophthalmic use only.
Information for Patients
The emulsion from one individual single-use vial to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

RESTATIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS® ophthalmic emulsion.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility**
Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 2-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/d, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study conducted at 0.5, 2, and 8 mg/kg/d, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 1000 and 500 times greater, respectively, than the daily human dose of one drop (28 μL) of RESTASIS® BID into each eye of a 60 kg person (0.001 mg/kg/d), assuming that the entire dose is absorbed.

Cyclosporine has not been found mutagenic/genotoxic in the Ames test, the V79-HGPRT test, the micronucleus test in mice and Chinese hamsters, the chromosome aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes in vitro gave indication of a positive effect (i.e., induction of SCE).

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/d (approximately 15,000 times the human daily dose of 0.001 mg/kg/d) for 9 weeks (male) and 2 weeks (female) prior to mating.

**Pregnancy-Teratogenic Effects**

Pregnancy category C.

**Teratogenic Effects:** No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine up to 300 mg/kg/d during organogenesis. These doses in rats and rabbits are approximately 300,000 times greater than the daily human dose of one drop (28 μL) of RESTASIS® BID into each eye of a 60 kg person (0.001 mg/kg/d), assuming that the entire dose is absorbed.

**Non-Teratogenic Effects:** Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/d and rabbits at 100 mg/kg/d), cyclosporine oral solution, USP was embryotoxic- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 30,000 and 100,000 times greater, respectively, than the daily human dose of one drop (28 μL) of RESTASIS® BID into each eye of a 60 kg person (0.001 mg/kg/d), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/d or 50 mg/kg/d, respectively, during organogenesis. These doses in rats and rabbits are approximately 17,000 and 30,000 times greater, respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/d oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 45,000 times greater than the daily human topical dose, 0.001 mg/kg/d, assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/d (15,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of RESTASIS® in pregnant women. RESTASIS® should be administered to a pregnant woman only if clearly needed.

**Nursing Mothers**
Cyclosporine is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of RESTASIS® ophthalmic emulsion, caution should be exercised when RESTASIS® is administered to a nursing woman.

**Pediatric Use**
The safety and efficacy of RESTASIS® ophthalmic emulsion have not been established in pediatric patients below the age of 18.

**Geriatric Use**
No overall difference in safety or effectiveness has been observed between elderly and younger patients.

**ADVERSE REACTIONS**
The most common adverse event following the use of RESTASIS® was ocular burning (7%). Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

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Before reading on, please see p. 74 for presenting complaint, history and examination.

Diagnosis, Workup and Treatment

Review of the patient’s original CT scan demonstrated soft tissue abnormalities inconsistent with TED (See Figure 2). Because of these atypical findings, additional laboratory testing and neuroimaging was ordered. Thyroid function tests were within normal limits, as were thyroid stimulating immunoglobulin (TSI), angiotensin converting enzyme, and anti-neutrophil cytoplasmic antibody (ANCA). MRI showed enlarged right medial and inferior rectus muscles, with significant irregularity of the intraconal soft tissue (See Figure 3). On the left, there was enlargement of the medial rectus with nodularity of the muscle contour.

Given the atypical clinical and radiologic findings and lack of thyroid dysfunction, the patient underwent right orbitotomy with biopsies of the involved orbital fat and inferior rectus muscle.

Histopathology demonstrated an atypical lymphoid proliferation (See Figure 4). Flow cytometry confirmed a population of surface kappa-biased B cells positive for CD19 and CD20, and negative for CD5 and CD10. This was consistent with an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (EMZL/MALT). The patient underwent PET/CT imaging for staging and was referred to an oncologist for further management. The PET/CT revealed increased standardized uptake values (SUVs) in the region of the extraocular muscles in addition to the left axillary lymph nodes, consistent with stage T2a EMZL/MALT.

Because of the stage of his disease, the patient underwent three cycles of systemic therapy with rituximab and bendamustine. Orbital swelling clinically improved and a repeat PET/CT demonstrated a decrease in both size and SUVs of the extraocular muscles and left axillary lymph nodes.
Discussion

The American Thyroid Association predicts that 12 percent of the U.S. population will develop thyroid dysfunction at some point in their lifetime. Depending on diagnostic criteria, up to 50 percent of patients with thyroid dysfunction will develop TED. Patients with TED may be euthyroid at presentation, but 25 percent will develop laboratory-confirmed thyroid dysfunction within one year, and 50 percent will do so within five years. Importantly, approximately 90 percent of patients with TED will demonstrate upper eyelid retraction on clinical exam, a feature notably absent in our patient.

Although extraocular muscle pathology is often associated with thyroid dysfunction, it is important to consider other causes, such as inflammatory, vascular, or neoplastic processes. In a series by Lynnette Watkins, MD, and colleagues, 45 cases of lymphoma of the extraocular muscles were described. The most common presenting signs were proptosis (53 percent), extraocular motility limitation (32 percent) and ptosis (14 percent). The most common symptom was diplopia (34 percent). Eighty-six percent of these lymphomas were B cell and 44 percent of these were EMZL/MALT. At presentation, four patients had lymph node involvement and six patients had widespread disease. Interestingly, almost 10 percent of patients were previously misdiagnosed as either TED or idiopathic orbital inflammation.

Ocular adnexal lymphoma is a monoclonal proliferation of lymphoid cells, usually of B-cell origin. This is postulated to occur from dysregulation in immunomodulation and chromosomal mutations that eventually select for a predominant monoclonal population. The process appears to be tied to either chronic antigenic stimulation or autoimmune disease. Monoclonality derives from a precursor B-cell (or T-cell) at a specific phase of maturation. Lymphoma subtypes can be classified according to the recently updated 2008 WHO classification. Importantly, each lymphoma subtype carries independent prognostic and treatment implications and should be considered as a distinct entity. Put succinctly, indolent ocular adnexal (OA) EMZL/MALT differs significantly from more aggressive and life-threatening subtypes, such as diffuse large B-cell and mantle cell lymphomas.

EMZL/MALT occurs at a median age of 65 years and most commonly involves the orbit, followed by the conjunctiva, lacrimal gland and eyelid. As mentioned, it typically has an indolent course, lacks systemic involvement at diagnosis and carries a favorable prognosis. However, outcomes are dependent on stage at diagnosis, and distant relapse is not uncommon. Corticosteroids can mask clinical presentation and histopathology, potentially resulting in a delay in definitive diagnosis. Various treatments for OA-EMZL/MALT are available, but no optimal treatment approach has been defined. For localized OA-EMZL/MALT, radiation therapy is typically utilized. For patients with regional extension or widespread disease, systemic chemotherapy is administered as either single-agent or combination therapy.

Newer therapies include immunotherapy (e.g., rituximab) and radioimmunotherapy, with further investigations under way. It is also important to remember that since OA-EMZL/MALT tends to follow a relatively indolent course in some fragile, elderly patients with significant comorbidities, conservative observation is an acceptable alternative to systemic therapy. Ultimately, the single most important feature in the management of OA lymphoma is the subtype of the tumor.

Given the ubiquity of thyroid dysfunction in the general population and the fact that the majority of extraocular muscle enlargement is indeed due to TED, it is not surprising that ophthalmologists generally ascribe all muscle enlargement to TED.

Alternative diagnoses should be considered when the patient exhibits atypical clinical or radiologic features, including persistent euthyroidism, lack of upper eyelid retraction or adduction deficits on extraocular motility examination (the vast majority of TED external ophthalmoplegia presents with some combination of abduction and vertical duction deficits). Atypical radiologic features on CT or MRI include isolated lateral rectus muscle enlargement, nodularity of the enlarged muscles (“bumpy muscles”) or significant infiltration of the intraconal fat. In such cases, biopsy of the involved tissue should be strongly considered before instituting empiric corticosteroid or radiotherapy.

The author would like to thank Jurij R. Bilyk, MD, of the Oculoplastic and Orbital Surgery Service and Ralph C. Eagle Jr., MD, of the Ocular Pathology Service.

1. American Thyroid Association: www.thyroid.org/about/
pressroom.html.
Seeking a second opinion, a patient presents to Wills Eye with bilateral lower lid swelling, ‘bulging’ eyes and diplopia.

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Presentation

A 55-year-old Hispanic male presented to the Wills Eye Institute’s Oculoplastic and Orbital Surgery Service for a second opinion regarding bilateral lower lid swelling, “bulging” eyes and diplopia. Two years prior, he had been diagnosed with thyroid eye disease (TED) by an outside ophthalmologist and treated with a six-month course of oral prednisone. Initial thyroid function tests were within normal limits. While tapering the oral corticosteroids over the ensuing 18 months, the patient experienced a flare of symptoms. When orbital radiation therapy was recommended, the patient elected to seek a second opinion from the Wills Eye Institute.

Medical History

Past medical history was significant only for borderline diabetes and allergic rhinitis. Family history was significant for diabetes and thyroid disease. The patient was a lifelong nonsmoker, but did consume a moderate amount of alcohol. Medications included cetirizine and aspirin. Review of systems was otherwise negative.

Examination

Ocular examination revealed an uncorrected visual acuity of 20/40 in each eye. Pupils were equal, reactive and without a relative afferent pupillary defect. Ishihara color plates were 8/8 briskly in each eye. Intraocular pressure measured with applanation tonometry was 24 mmHg in each eye, increasing to 36 mmHg in upgaze.

Bilateral lower lid festooning was present but there was no obvious upper lid retraction. He displayed bilateral lagophthalmos and inferior chemosis. Resistance to retropulsion was increased, more so on the right side. Hertel exophthalmometry confirmed symmetric proptosis of 29 mm bilaterally measured with a base of 96 mm. A right hypertropia was present in primary gaze with restricted extraocular motility bilaterally (See Figure 1).

Dilated funduscopic examination showed anomalous discs but no evidence of disc edema, venous congestion or chorioretinal folds. Automated perimeter was normal on both sides.

Figure 1. On external examination, the patient displays chemosis, lower lid festooning and right hypertropia. Note the distinct absence of upper eyelid retraction. The patient demonstrates restriction in upgaze OS, in downgaze OU and, atypically, in adduction OS.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 72
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