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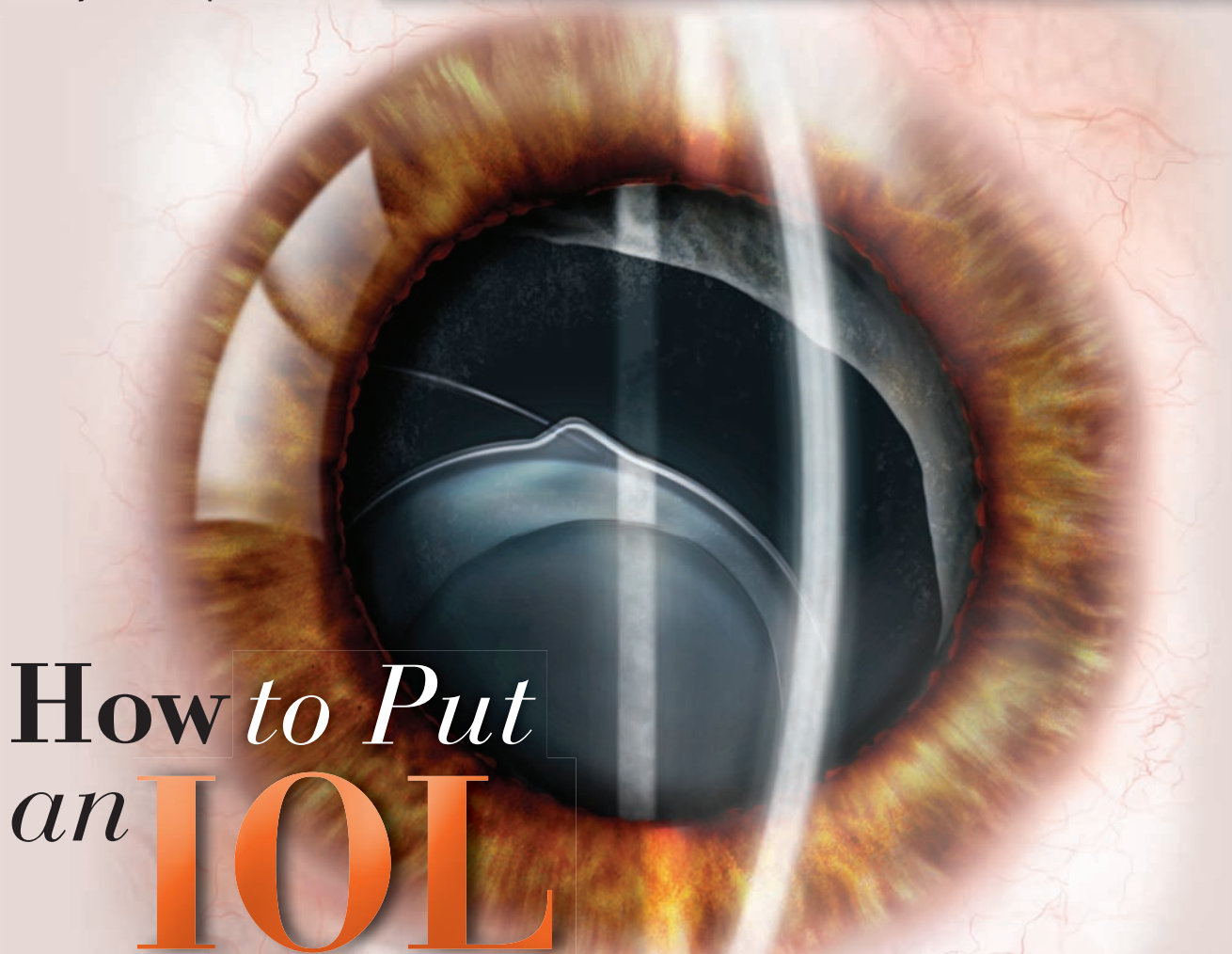

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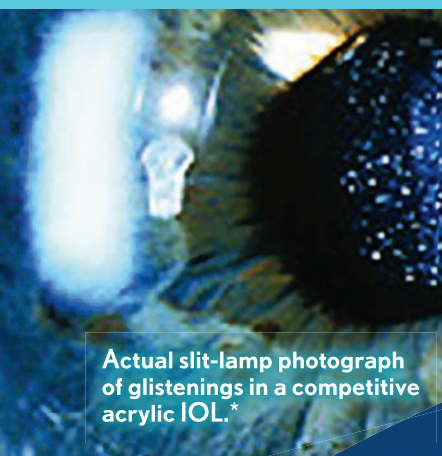
jmi

Glistenings do exist.



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1. Bausch & Lomb Incorporated Study #658 - "A Prospective Multicenter Clinical Study to Evaluate the Safety and Effectiveness of a Bausch + Lomb One Piece Hydrophobic Acrylic Intraocular Lens in Subjects Undergoing Cataract Extraction." Final Clinical Study Report, dated 24 Aug 2011. **2.** Tetz MR, Werner L, Schwahn-Bendig S, Batlle JF. A prospective clinical study to quantify glistenings in a new hydrophobic acrylic IOL. Presented at: American Society of Cataract and Refractive Surgery (ASCRS) Symposium & Congress; April 3-8, 2009; San Francisco, CA. **3.** enVista™ Directions for Use. **4.** Santhiago MR, Netto MV, Barreto J Jr, et al. Wavefront analysis, contrast sensitivity, and depth of focus after cataract surgery with aspherical intraocular lens implantation. *Am J Ophthalmol.* 2010;149(3):383-389. **5.** Pepose JS, Qazi MA, Edwards KH, Sanderson JP, Sarver EJ. Comparison of contrast sensitivity, depth of field and ocular wavefront aberrations in eyes with an IOL with zero versus positive spherical aberration. *Graefe's Arch Clin Exp Ophthalmol.* 2009;247(7):965-973. **6.** Johansson B, Sundelin S, Wikberg-Matsson A, Unsbo P, Behndig A. Visual and optical performance of the Akreos® Adapt Advanced Optics and Tecnis Z9000 intraocular lenses: Swedish multicenter study. *J Cataract Refract Surg.* 2007;33(9):1565-1572. **7.** Nishi O, Nishi K, Osakabe Y. Effect of intraocular lenses on preventing posterior capsule opacification: design versus material. *J Cataract Refract Surg.* 2004;30(10):2170-2176.

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REVIEW NEWS
Volume XX • No. 1 • January 2013

Prevalence of Visual Impairment in U.S. Increases

The prevalence of nonrefractive visual impairment in the United States has increased significantly in recent years, which may be partly related to a higher prevalence of diabetes, an associated risk factor, according to a study in the December 12 issue of the *Journal of the American Medical Association*.

It is estimated that more than 14 million individuals in the United States aged 12 years and older are visually impaired (<20/40). Of these cases, 11 million are attributable to refractive error. In the United States, the most common causes of nonrefractive visual impairment are age-related macular degeneration, cataract, diabetic retinopathy glaucoma and other retinal disorders, according to the article. Previous studies have shown that visual impairment is common in persons with diabetes. "The prevalence of diagnosed diabetes has increased among adults in recent years, rising from 4.9 percent in 1990 to 6.5 percent in 1998, 7.9 percent in 2001, 10.7 percent in 2007 and 11.3 percent in 2010," the authors write.

Fang Ko, MD, of the Johns Hopkins University School of Medicine, and colleagues conducted a study to assess the prevalence of nonrefractive visual impairment and factors associated with risk of visual impairment. The study included data from the National Health and Nutrition Examination Survey (NHANES), a representative sample of the U.S. population. In 1999 to 2002 and 2005 to 2008, 9,471 and 10,480 participants 20 years of age or older received questionnaires, laboratory tests and physical examinations. Visual acuity of less than 20/40 aided by autorefractor was classified as nonrefractive visual impairment.

The researchers found that prevalence of nonrefractive visual impairment increased 21 percent, from 1.4 percent in 1999 to 2002 to 1.7 percent in 2005 to 2008; and increased 40 percent among non-Hispanic whites 20 to 39 years of age, from 0.5 percent to 0.7 percent. In analysis among all participants, factors associated with nonrefractive visual impairment included older age, poverty, lower education level and diabetes diagnosed 10 or more years ago. Among these risk factors, only the latter has increased in prevalence between the two time periods considered. Prevalence of diabetes with 10 or more years since diagnosis increased 22 percent overall from 2.8 percent to 3.6 percent; and 133 percent among non-Hispanic whites 20 to 39 years of age, from 0.3 percent to 0.7 percent.

"We report a previously unrecognized increase of visual impairment among U.S. adults that cannot be attributed to refractive error," the authors write. "If the current finding becomes a persisting trend, it could result in increasing rates of disability in the U.S. population, including greater numbers of patients with end-organ diabetic damage who would require ophthalmic care. These results have important implications for resource allocation in the debate of distribution of limited medical services and funding. Continued monitoring of visual disability and diabetes, as well as additional research addressing causes, prevention and treatment, is warranted."

Glaucoma Testing Lags In Hispanics

The odds of individuals with open-angle glaucoma undergoing visual field testing decreased for all racial/ethnic groups from 2001 through 2009, but the odds decreased the most for Hispanic men and women in a study of enrollees in a large U.S. managed-care network, according to a report published in the December issue of *Archives of Ophthalmology*.

Open-angle glaucoma is more prevalent in racial minorities compared with whites, and racial minorities are more likely to experience vision loss and blindness from OAG, according to the study background.

Joshua D. Stein, MD, MS, and colleagues at the University of Michigan, Ann Arbor, examined whether racial disparities exist in the use of ancillary testing to evaluate individuals with open-angle glaucoma. The researchers identified all enrollees

age 40 years and older in a large managed care network who had retinal or optic nerve conditions that could warrant ancillary testing.

Among the 797,879 eligible enrollees, 149,018 individuals had open-angle glaucoma. The researchers performed statistical analyses to determine the odds and probabilities each year of undergoing visual field testing and other procedures for black (n=15,905), white (n=118,062), Hispanic (N=9,376) and Asian-American (n=4,350) men and women and then compared the groups, according to the study.

The odds of undergoing visual field testing decreased for all groups from 2001 through 2009, decreasing most for Hispanic men and women (63 percent and 57 percent, respectively) and least (36 percent) for Asian-American men. By comparison, the odds of undergoing other ocular imaging increased for all groups from 2001 through 2009, increasing most (173 percent) for black men and women and least (77 percent) for Hispanic women, according to the study results.

"While it is encouraging that black individuals are receiving similar or greater levels of monitoring of OAG relative to white individuals, it is disconcerting that there are significant disparities in glaucoma testing among the Hispanic population, the fastest growing racial minority in the United States," the authors comment.

The authors note that further research should focus on reducing racial disparities.

"Although increases in glaucoma testing have been noted in recent years among Hispanic men and women for some types of ancillary tests, efforts should be made to better understand and overcome some of the persistent barriers to monitoring for glaucoma in this group," they conclude.

New Technique to Deliver Stem Cells To the Cornea

In research published in the journal *Acta Biomaterialia*, researchers from the University of Sheffield, South Yorkshire, England, describe a new method for producing membranes to help in the grafting of stem cells onto the eye, mimicking structural features of the eye itself. The technology has been designed to treat damage to the cornea, which is one of the major causes of blindness in the world.

Using a combination of techniques known as microstereolithography and electrospinning, the researchers are able to make a disc of biodegradable material that can be fixed over the cornea. The disc is loaded with stem cells which then multiply, allowing the body to heal the eye naturally.

"The disc has an outer ring containing pockets into which stem cells taken from the patient's healthy eye can be placed," says EPSRC Fellow, Ílida Ortega Asencio, from Sheffield's Faculty of Engineering. "The material across the center of the disc is thinner than the ring, so it will biodegrade more quickly allowing the stem cells to proliferate across the surface of the eye to repair the cornea."

A key feature of the disc is that it contains niches or pockets to house and protect the stem cells, mirroring niches found around the rim of a healthy cornea. Standard treatments for corneal blindness are corneal transplants or grafting stem cells onto the eye using donor human amniotic membrane as a temporary carrier to deliver these cells to the eye. For some patients, the treatment can fail after a few years as the repaired eyes do not retain these stem cells, which are required to carry out ongoing repair of the cornea. Without this constant repair, thick white scar tissue forms across the cornea causing partial or complete sight loss. The researchers have designed the small pockets they have built into the membrane to help cells to group together and act as a useful reservoir of daughter cells so that a healthy population of stem cells can be retained in the eye.

"Laboratory tests have shown that the membranes will support cell growth, so the next stage is to trial this in patients in India, working with our colleagues in the LV Prasad Eye Institute in Hyderabad," says Professor Sheila MacNeil. "One advantage of our design is that we have made the disc from materials already in use as biodegradable sutures in the eye so we know they won't cause a problem in the body. This means that, subject to the necessary safety studies and approval from Indian Regulatory Authorities, we should be able to move to early stage clinical trials fairly quickly."

Glaucoma Study Could Inspire E-Reader Apps

Adults with glaucoma read slower when reading silently for long periods of time and are more likely to have their reading speed decrease over time, possibly a result of reading fatigue, according to a new study in *Investigative Ophthalmology & Visual Science*

Technological solutions such as e-readers and apps could help. "Right now, so many products are available for presenting reading material in a variety of formats," says author Pradeep Ramulu MD, PhD, of the Wilmer Eye Institute, Johns Hopkins Hospital. "If the optimal format for reading in the context of glaucoma could be determined, it would be

easy to create an application to present text in this manner as part of a commercial device such as an iPad or Kindle."

The article reports that the sustained silent reading speed for glaucoma patients with bilateral visual field loss is significantly less than the speed associated with out-loud reading.

The study was conducted with two groups from the Wilmer Eye Institute: patients with bilateral VF loss from glaucoma and the control group made up of glaucoma suspect patients. Both groups were evaluated using two out-loud reading tests (IReST and MNRead), a sustained silent reading test over a 30-minute period and a comprehension evaluation corresponding to the sustained silent reading material. On the IReST evaluation, those with glaucoma read 147 vs. the control group 163 words per minute; on the MNRead, those with glaucoma read 172 vs. the control group 186 wpm; and on the sustained silent reading test, those with glaucoma read 179 vs. the control group 218 wpm—a 16 percent slower reading speed.

The results also showed that reading comprehension was lower in the glaucoma group than the control group. Though this finding fell just outside the cutoff for statistical significance, the research team suggests further studies be conducted to investigate whether visual defects or coexisting cognitive defects are the cause.

"The ultimate goal is to be able to rehabilitate individuals with reading difficulties due to glaucoma," says Dr. Ramulu. "Our group and others are exploring possible reasons behind these impairments, including disruption of the tear film and aberrant eye movements. Understanding why people with glaucoma read slower and show reading fatigue will pave the way for solving these reading difficulties." REVIEW

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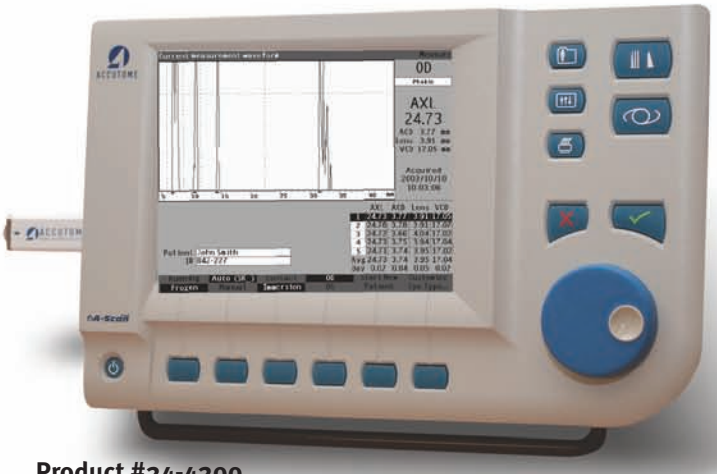

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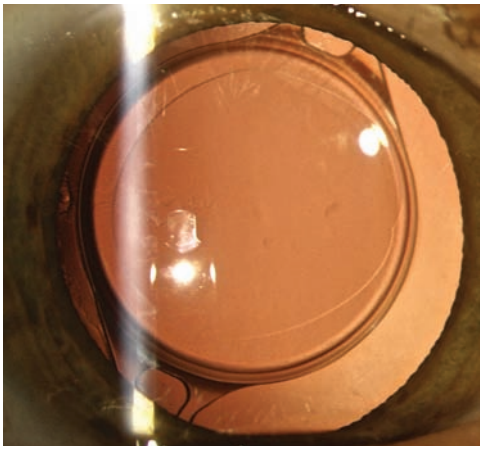

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REVIEW Editor's Page

Christopher Glenn, Editor in Chief

Moving on, But Not Alone

A man learns he will soon die and goes to visit his friends to seek help. The first explains, "I can't help you after you die." Unsatisfied, he goes to the second. This one offers to arrange for his friend's funeral and burial, but says that after the man is gone, "I can't have any more to do with you."

More desperate, he seeks out a third friend, one he hadn't thought of often or paid much attention to.

"Yes, I can help you," the friend says. "Even after I'm gone?" the man asks. "Yes, I'll be with you always."

The first friend, according to this parable attributed to the Prophet Muhammad, is wealth. The second is family and friends. The third, the deeds and actions of the man's lifetime, which will accompany him after he has left this life.

This page is always devoted to issues that in my humble view may be of concern to our physician readers. This month, a slightly different tack.

Not all that many years ago, you could not find a publication like this one in ophthalmology. As in most medical subspecialties, there were a number of peer-reviewed journals, and a couple of tabloid-style news publications. But the idea of an advertising-supported magazine, with more of a feature-article approach to editorial, simply didn't exist. Thanks in large part to the efforts of founding publisher Rick Bay, that changed in 1994 with the launch of the Review.

As we begin our 20th year, we do so without our friend, our mentor and our leader, as Rick succumbed in early December to a long illness.

As publisher, Rick headed the business side of the Review, managing the advertising and other revenue-producing projects that keep us afloat, so his is not likely a name most readers will recognize. To advertisers and those on the industry side, he was not only well-known, but highly respected and trusted. We have heard from so many of them since early December.

Their tributes and remembrances reflect, even amplify, the truth in the Prophet's parable: Rick has moved on, but not alone. He takes with him the love, the respect and the friendship that he spent his career cultivating, in the hundreds who worked for him over the years, and in the clients whose needs he served so well.

Whether you knew him or not, the admiration he held for the work that ophthalmologists do every day to make their patients' lives better was an important motivation for Rick. He considered it a privilege to serve you. The magazine you hold in your hands is testament to that.

Vaya con Dios, Babe.

Praising 'Myths,' & an Epinephrine Shortfall

To the Editor:

I absolutely loved your article on "myths." ("Common Wisdom: Science or Myth?" November 2012) I loved it for several reasons. First of all, I thought it was courageous of you even to suggest that a significant portion of physician behavior is based on poor evidence. Every time I hear about the importance of "evidence-based medicine," I want to scream, because as it is used it is virtually always self-adulatory. I don't see that physicians are any more interested in evidence now than they ever have been in the history of mankind. They just want to use evidence that they like, and that they find confirms their own biases. The examples you gave were interesting and appropriate.

Many years ago, a brilliant physicist, Sherman Frankel, pointed out to me that physicians were painfully unaware of systematic bias. His comment started me off on a great deal of thinking, then research. He is absolutely right. Systematic bias is a major, major, major problem in medical care.

Examples of systematic bias include the following: When in doubt whether to treat or not, treat! If a finding is "within normal limits," that's good. People with the same diagnosis. "The doctor knows best." The more tests the better. Physicians are more altruistic and freer from bias than other people. And, dishonesty is okay as long as the physician believes that the reason he or she is being dishonest is because it is in the best interest of the patient.

These phrases describe the way physicians act. There is as much or more evidence indicating these beliefs are incorrect as there is that they are valid.

The items that you list in your article are not truly myths. They are unsubstantiated opinions. A myth is a belief that drives fundamental aspects of behavior. Many myths are fervently believed by many people, such as the idea that God created the world over a period of seven days and that if you die in battle (and are on the right side) you go immediately to Valhalla, the warriors' heaven. A scientific definition of a myth could be a systematic bias. I am grateful to Dr. Frankel for making me aware of my systematic biases. Now, if only I could figure out which ones are valid!?

Sincerely,
George Spaeth, MD
Louis J. Esposito Research Professor
Wills Eye Institute
Philadelphia

To the Editor:

Now we no longer can access commercial preservative-free (free of sodium bisulfite) intraocular epinephrine. In recent years, we have been plagued by shortages of other pharmaceuticals.

I do not see any sign that our representatives of organized medicine or ophthalmology are explaining this problem, let alone addressing and helping to solve this problem.

I am as much a conspiracy buff as the next person, but I do not see any benefit to anyone if something is not being sold. I do not think anyone gains anything; I doubt that the compounding pharmacies are conspiring so that the commercial manufacturers will suddenly, and inexplicably, have epinephrine on back order.

These shortages are challenging our ability to provide optimal patient care. They're episodic and recurrent, and affect all categories of medications. Perhaps one of the major ophthalmic drug companies will undertake to manufacture a menu of these items, in the interest of doctor loyalty and patient safety.

Yours sincerely,
Samuel M. Salamon, MD
Euclid, Ohio

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Striving to Improve Intravitreal Injections

Two devices aim to make this increasingly common procedure safer, quicker, more consistent and less expensive.

Christopher Kent, Senior Editor

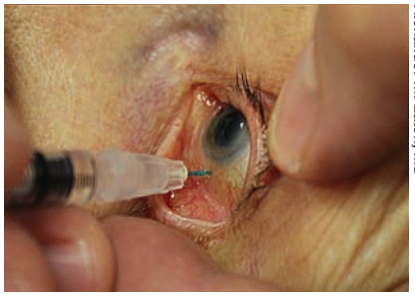
Any new device or technique that makes intravitreal injections simpler or safer is usually welcome. Two novel devices may help accomplish that goal—one by preventing contamination of the needle before the injection, the other by reducing the amount of equipment required during the procedure and standardizing the injection process.

Protecting the Needle

Alexander M. Eaton, MD, director of the Retina Health Center in Fort Myers and Naples, Fla., has helped develop a single-use "guarded injection device"—a tiny, collapsible sleeve that protects the needle from exposure to contaminants such as aerosolized saliva prior to and during the injection. "The needle comes with the sleeve already on it," Dr. Eaton explains. "The surgeon draws the drug up with whatever needle he prefers; he then replaces it with the guarded needle for the injection.

"The sleeve covers the entire needle shaft except for a little opening at the end that allows the surgeon to place the shaft against the eye," he continues. "The shaft is protected from aerosolized saliva in case the patient or surgeon speaks, as well as from contamination from blinking or movement. The guard collapses as the needle advances; it remains outside the eye, keeping the needle sterile during the entire injection process."

Dr. Eaton notes that the sleeve should eliminate the need for a lid speculum, particularly in patients who receive topical anesthetics. "When topicals are used you can never be completely certain that patients won't squeeze or move when you give the injection. This device will prevent any contamination of the needle should that happen. This also has other benefits: Not needing a speculum reduces the amount of time required for the injection, and should also help reduce the risk of corneal abrasions and drying. Furthermore, it should save staff time because it eliminates the need to process and prepare the speculum."



Alexander M. Eaton, MD

This "guarded injection device" covers the needle with a collapsible, protective sleeve that remains outside the eye.

Dr. Eaton says he conducted a limited pilot study with 70 patients to compare the time required to do an injection in the traditional way (with a lid speculum) to the time required when the needle sleeve was used. "We measured the time from the instant the speculum or guarded needle was picked up to the moment the injection was completed and the instruments disposed of. Using the device, the injections took 23 ±8.2 seconds; done the traditional way, the injections took 34.4 ±5.7 seconds. The difference was highly statistically significant. We also measured the processing time for the speculum when it was used; that averaged 5 minutes and 28 seconds, which did not include autoclaving time.

"It's worth noting that this timing was measured in a research setting with a trained assistant and all the equipment prepared," he continues. "In real clinical use, the difference in

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time when using the sleeve may be even greater. Things are not always perfectly arranged when the surgeon enters the room." Dr. Eaton notes that the data also showed a trend toward patients finding the guarded needle injections to be more comfortable than the traditional injections—due, at least in part, to not using a speculum.

Dr. Eaton acknowledges that it will be almost impossible to prove that the device reduces the rate of endophthalmitis, but he has done a study that suggests it might. "To test the effectiveness of the sleeve, we created 'model eyes' by filling sterile, empty Lucentis and Eyelea bottles with broth," he explains. "Then we contaminated the outside of protected and unprotected needles with saliva and inserted them into the bottles.

"The bottles that were injected with unprotected needles all developed bacterial growth within 72 hours, while none of the others did," he notes. "All the bacteria were in the *Streptococcus viridans* group—the most common cause of strep infection following intravitreal injections. *Streptococcus* is very virulent, which is why the visual outcomes with post-intravitreal-injection endophthalmitis have generally been poor."

In terms of downsides, Dr. Eaton says adding the sleeve to the needles will undoubtedly increase the cost. "Our goal is to keep the cost difference very modest," he says. "We hope to have the guarded needles available in the marketplace within six months to a year."

Standardizing the Injection

The disposable InVitria injection assistant (FCI Ophthalmics) is designed to help make intravitreal injections simpler, faster and more predictable. It consists of a polycarbonate shell that's placed over the eye, with a guide tube into which the syringe is placed. A flange on the side of the device prevents any lashes from getting into the field, eliminating the need for a speculum.

FCI Ophthalmics

The InVitria device standardizes the angle, depth and location of each injection, while eliminating the need for a speculum.

Once the device is aligned over the limbus (using a positioning line on the instrument), the device is rotated to create a stepped incision profile. The gentle downward pressure of the device fixates the eye while creating an anesthetic effect. During the injection the guide ensures that the needle enters the eye at a 28-degree angle with the needle reaching a depth of 5.6 mm, exactly 3.5 mm from the limbus. Further rotation of the device prior to removing it from the eye prevents vitreous prolapse because of the conjunctival displacement.

Gokulan Ratnarajan, MBBS, who practices at The Royal Berkshire Hospital, Reading, U.K., has used the device for several months. (Neither he nor the institution has any financial interest in the device.) "When we were approached by the company to try the instrument it looked like a good idea, but we wanted to do a small pilot study," he says. "So we compared 100 patients who received the injections by a conventional technique to 100 patients whose injections were performed with the aid of the device."

In the study, researchers monitored patient pain scores, patient preference, surgeon perception regarding ease of insertion and the relative costs of the two approaches. The visual analogue pain scale score (from 0=no pain to 10=unbearable pain) in the conventional group was 2.58, compared to 1.38 in the InVitria group ($p<0.01$); the surgeon ranked the insertion of the device as easy in 89 cases, moderately difficult in 10 cases, and difficult in one case; and using the device cost about $12.35 less than using a conventional pack, which would amount to an annual savings of nearly $40,000 at the hospital.

"Patients liked the fact that they didn't have a drape over their faces," he notes. "And the hospital liked the fact that it was cheaper than the pre-made injection packs because less equipment, such as the surgical drape, calipers and disposable forceps, was required. Furthermore, in my experience, the learning curve for this device was simple and quick. I felt comfortable using it straightaway."

Dr. Ratnarajan believes the device could be particularly useful if intravitreal injections are routinely given by health professionals other than the surgeon. "A device such as this might be less beneficial for an experienced surgeon, but for other health professionals or surgeons who are learning it could make injections safer and more consistent," he says. "Either way, you still have the improved patient experience and cost savings."

Regarding safety, Dr. Ratnarajan notes that their study is too small to draw any firm conclusions. "We didn't have any major complications in either group, but you'd need a much bigger study to comment on that with any authority," he says.

"Ultimately, we published our study in the *British Journal of Ophthalmology*," he adds. "Our study does suggest that this instrument has value. We have now adopted it throughout the Institute and we're very happy with it." REVIEW

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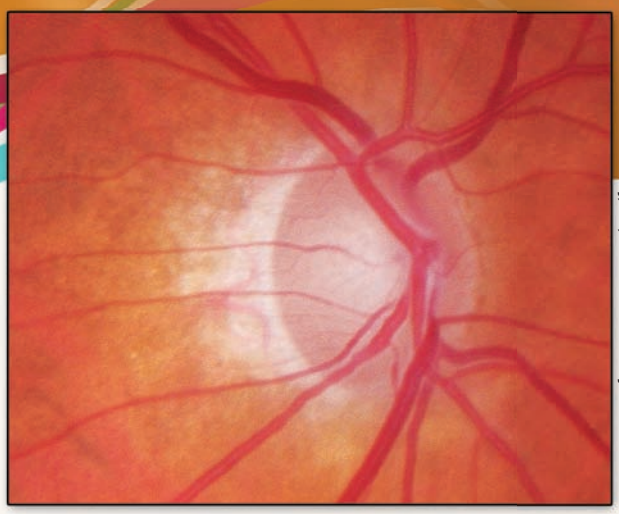

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Toric IOLs: Nailing The Alignment

Christopher Kent, Senior Editor

The art of perfecting toric IOL orientation continues to evolve—with ever-improving outcomes.

As toric intraocular lenses become more popular, accurate alignment of the lens inside the eye remains a key concern. "For every degree of misalignment, about 3 percent of the lens cylinder power is lost," notes Soosan Jacob, MD, a senior consultant ophthalmologist at Dr. Amar Agarwal's Eye Hospital in Chennai, India. "If it's 30 degrees off, it's a total loss—the lens will have zero effect. If you're more than 30 degrees off, you're actually increasing the patient's postoperative astigmatism."

Accurate alignment is a function of several factors, including accurate measurement of the astigmatic axis, accurately locating that axis in the eye, placing the lens correctly and preventing or correcting any postoperative misalignment. Here, four experienced surgeons share their advice on getting toric IOL alignment right.

Finding the Axis: A New Factor

Identifying the axis, even in cases of regular astigmatism, is not as straightforward as it seems. "There's variability in everything," notes James A. Davison, MD, FACS, who practices at the Wolfe Eye Clinic in Marshalltown and West Des Moines, Iowa. "Some people have zero diopters of keratometric astigmatism but still have some significant cylinder in their refraction. Some have keratometric astigmatism, but they don't choose cylinder correction in the manifest refraction."

Reflecting that complexity, Dr. Davison, like some of his colleagues, noted that something unexplained was happening with some of his toric patients. "We found patients were sometimes coming out slightly undercorrected or overcorrected, for no obvious reason," he says. "We realized that most keratometry and topography are just based on the anterior reflection of the anterior surface of the cornea. However, the Pentacam has a measurement called 'total corneal refractive power' that also takes into account the posterior surface of the cornea. We found that this produced a slightly different measurement. For example, the sagittal anterior reflection measurement from the Pentacam might indicate that we should use a T4 lens, but the total corneal refractive power might back it off to a T3 lens.

"So we began checking in the clinic to see whether the outcomes were better if the correction was based on the Pentacam's total corneal refractive power measurement, and how it compared to the outcomes using keratometry from the IOLMaster and Lenstar," he continues. "We haven't analyzed all of our data yet, but our

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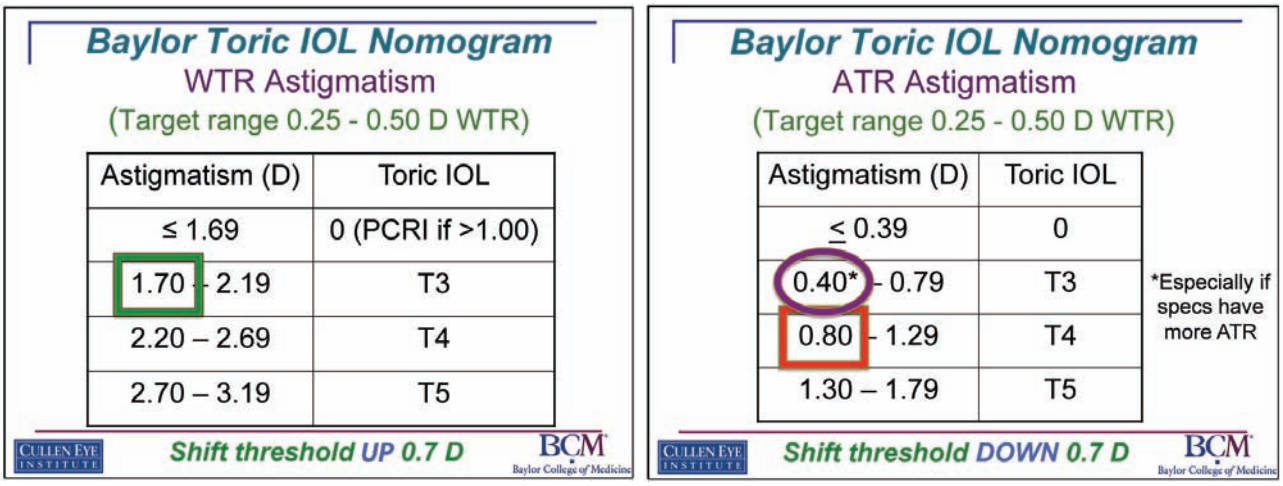


Douglas D. Koch, MD

This nomogram offers a way to compensate for the against-the-rule astigmatism added to the refraction by the posterior surface of most corneas. Left: If the patient has with-the-rule astigmatism, the threshold for using a toric IOL is shifted up 0.7 D, so the surgeon would not choose a T3 lens until the anterior corneal astigmatism is 1.7 D. (Amounts down to 1 D can be treated with peripheral corneal relaxing incisions [PCRI].) Right: If the patient has against-the-rule astigmatism, the posterior corneal surface adds to that measured on the anterior surface. The surgeon should be more aggressive about selecting a toric IOL and shift the nomogram down 0.7 D. So, for a patient who has 0.4 D ATR (typically with more in the refraction), the surgeon could opt for a T3, switching to a T4 when the anterior ATR cylinder is 0.8 D.

impression is that we're getting better results using the total corneal refractive power measurement for with-the-rule, against-the-rule, and obliquely oriented astigmatism."

A similar experience led Douglas D. Koch, MD, professor of ophthalmology at Baylor College of Medicine in Houston, to uncover some key factors that can affect the outcome when implanting a toric IOL—both in the near and long term. "I had treated a patient who had with-the-rule astigmatism, and my measurements indicated that he should have come out a tiny bit undercorrected," he says. "Instead, he was overcorrected. At the same time, I treated another patient who started out with against-the-rule astigmatism; if anything, that patient should have ended up slightly overcorrected, but instead she was undercorrected. There was no obvious explanation.

"Prior to seeing those patients, I had started a study along with Li Wang and Mitchell Weikert in our group, looking at posterior corneal astigmatism," he continues. "We were curious to find out whether this was an issue. We weren't aware that the literature had already demonstrated that there was some astigmatism there. Our own research found a significant amount of posterior corneal astigmatism, and it has indeed turned out to be significant in our clinical use of toric lenses.

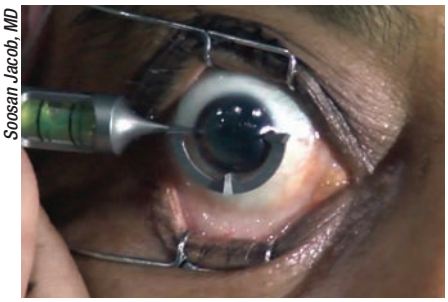
"We found that the posterior cornea is steeper vertically in almost everybody," he says. "Because it's a minus lens, it creates refractive power horizontally, or against-the-rule refractive power at 180 degrees. So the with-the-rule patient who was overcorrected had posterior corneal astigmatism that was adding to his against-the-rule refractive power. That's why he ended up overcorrected. And the patient who had the against-the-rule astigmatism had additional against-the-rule on the back, which is why she came out undercorrected."

Constructing a Nomogram

"After realizing this I began to look at other patients and found I was seeing this all the time," Dr. Koch continues. "Using the data from our Galilei Scheimpflug analyzer, we found an average of about a half diopter of posterior astigmatism when patients had with-the-rule on the front; and about 0.3 D when they had against-the-rule on the front. It does vary from patient to patient, so measuring it would be ideal. However, using those numbers, we were able to construct a basic nomogram for modifying the toric IOL selection to accommodate the posterior astigmatism." (Dr. Davison notes that his use of the total corneal refractive power from the Pentacam produces a modification that appears similar to Dr. Koch's posterior corneal astigmatism nomogram adjustment.)

Dr. Koch says he soon found another factor worth taking into account. "I came across a fascinating paper by Ken Hayashi, MD, in the *American Journal of Ophthalmology*, in which patients were followed for 10 years," he says. "His team followed two groups: One had no surgery, while the other had 3-mm clear corneal temporal incisions. Despite having temporal incisions, the latter patients gradually shifted toward against-the-rule astigmatism over 10 years by about 3/8 D, just like the unoperated eyes did.[1]

"What we've learned is that even though cataract surgery may be 'weakening' the cornea temporally, it doesn't protect you against the gradual


Soosan Jacob, MD

ASICO

Manual tools designed to help ensure that horizontal axis marks are level include devices with a bubble level (left) and devices with visual or auditory cues to indicate level placement such as the Akahoshi electronic toric IOL marker (A,B and C above).

against-the-rule shift that corneas undergo," he explains. "So, when deciding how to proceed with a toric IOL, my thought is that we should leave patients a little bit of with-the-rule so they can still have good vision over the years as they gradually shift against-the-rule."

Dr. Koch has constructed a nomogram that takes into account the average posterior corneal astigmatism in the with-the-rule and against-the-rule groups. *(See p. 21)* It also takes into account the need to leave these patients with a little bit of with-the-rule astigmatism to compensate for the gradual against-the-rule shift caused by aging. "Of course, you may vary how you choose to apply the nomogram according to the patient's age and other factors," he says. "For example, in my experience most patients who have oblique astigmatism are in that progressive march from with-the-rule to against-the-rule. For those patients I usually attempt to correct the astigmatism fully, but I target the correction about 5 degrees on the against-the-rule side, so it gives them a little time as they continue to shift."

Dr. Koch says it's still early in the refinement of the nomogram, although he has data that support it. "We have the data we gathered by measuring posterior corneal surfaces in virgin eyes, and now we have data on 41 eyes that have had surgery," he says. "The nomogram nails it. It's pretty amazing that we've been using toric lenses for several years, and we're just now figuring this out."

He notes that the manufacturers are aware of this issue, and they're in a bit of a dilemma. "The FDA understandably doesn't want manufacturers sending out nomograms that haven't been validated with FDA data," he says. "But I know that at least two manufacturers have looked at their data, and said, 'Oh my goodness—there it is.' "

Marking Freehand

Marking the eye is a potential source of error, for many reasons. Tools to increase accuracy are proliferating, as are high-tech approaches that hope to circumvent the need to make a mark altogether. Nevertheless, like many surgeons, Dr. Davison prefers to mark the eye freehand. His preference is to make a mark at 6 o'clock on the conjunctival limbus using a fine-tip marker. "The fine-tip marker makes a pretty small dot," he notes, "in contrast to a medium tip marker that can make a dot that's 10 degrees wide, or a small tip, which makes a dot that's probably about three degrees wide.

"In surgery we put the speculum in and put some more drops in," he continues. "Then we line the axis marker up with the 6:00 dot and make sure everything looks perfectly spaced around the limbus, so we're not eccentric. Then we take the axis marker and mark the intended axis. Once that's done and everything looks perfect, I dry the cornea a little at the periphery and I take a Weck-Cel sponge with ink on it and reinforce the intended axis mark to ensure it won't wash away. After that it's just a matter of putting in the lens and getting it to the right spot.

"Once the lens is in, I get all of the viscoelastic out from behind and in front of the lens," he says. "Then I rotate the lens so it's 10 to 15 degrees from the intended alignment, reinflate the eye, hydrate the incision and try to get everything looking nice and normal. I can usually go in with BSS on a 30-ga. cannula and move the lens to the final position. If too much fluid leaks out of the incision using the 30-ga. cannula, I can go in and do the rotation with the silicone irrigation/aspiration tip. You can actually suck on the anterior IOL optic with it, like a little plunger, and rotate the implant just like dialing an old-fashioned rotary telephone dial."

Tools for Better Marking

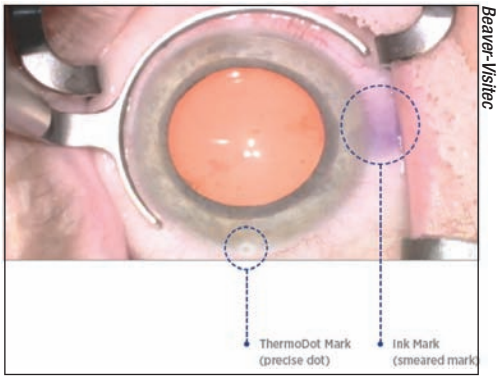
One method of freehand marking some surgeons prefer is putting two marks across from each other on the horizontal axis. However, Dr. Jacob notes that this is less than ideal. "It's difficult to put the marks exactly 180 degrees apart," she points out. "When the patient is lying down in the OR you may realize that your marks are not actually 180 degrees apart. Now you're left wondering which of the marks is closer to the axis—and it's likely that both of them are a bit off."

Dr. Jacob says she prefers to use one of the currently available devices that help ensure the correct placement of horizontal reference marks. "Several markers have a bubble level," she explains. "When the air bubble is exactly in the center of the two marks on the chamber, you know that the marker

is horizontally aligned. You ink the marker and gently apply it to the patient's eye while the patient is looking straight ahead, making sure the bubble shows the marker is horizontal. I use a drop of topical anesthetic and put a speculum on the eye; that allows me to concentrate on the bubble level without having to worry about keeping the patient's eye open.

"Sometimes using the bubble level is difficult because you have to keep an eye on the bubble while also looking at the limbus," she admits. "You don't want to cause a corneal epithelial abrasion while you're managing all this. However, some devices make this easier. ASICO now offers the Akahoshi electronic marker, which has three lights—red green and orange. When the marker is horizontal, the light is green; the other colors tell you which way you're tilted if you're not horizontal. The device can also provide an auditory cue when the marker is horizontal, so you don't have to look away from the eye to know when the orientation is correct. Most markers, including this one, come in two versions: One just makes the horizontal reference marks; the other allows you to directly mark the target axis for the IOL."

Robert H. Osher, MD, professor of ophthalmology at the University of Cincinnati, is a leading advocate of finding better ways to align toric lenses. "I dislike approaches that use ink to mark the eye," he says. "The ink diffuses and the results are inaccurate." He notes that one of the newest alternatives to marking the eye with ink is the Wet-Field Osher ThermoDot Marker from Beaver-Visitec. (He has no financial interest.) "The ThermoDot is a tiny dot created by a specially designed wet-field cautery tip, making an indelible mark on the target meridian," he explains. "So instead of using ink and having the mark diffuse or disappear, the tiny dot remains throughout the case. The device was released at this year's Academy of Ophthalmology meeting." (For more information, visit beaver-visitec.com/products/electrosurgery.cfm.)



Beaver-Visitec

The Wet-Field Osher ThermoDot Marker uses cautery to create a tiny, indelible mark to identify a chosen axis. Unlike ink, it can't blur or wash away.

The High-tech Approach

Dr. Osher has also worked with three high-tech tools designed to aid alignment, currently in different stages of development. "The first is iris imaging," he says. "I refer to this as fingerprinting. We take a photo of the iris, use software to overlay a protractor onto the image and then either inject it into the microscope view or print it. This approach is a little bit time-consuming, but it gives you extremely accurate orientation."

Dr. Osher notes that this method requires following a few basic principles. "Initially I tried orienting the lens by using the limbal vessels as landmarks," he says. "However, that doesn't work well when you dilate the pupils with neosynephrin because the vessels shrink up. In fact, some of the vessels dilate if you use preoperative topical antibiotics, so matching vessels can be challenging. Moreover, you can't have a picture of an undilated pupil and expect to get yourself well-oriented once the pupil is dilated in surgery. So, the image I take is a high-res photo when the patient is dilated during the original examination. Once I have that, there are many landmarks that make it very easy to get accurately oriented—crypts, nevi, unique patterns of stroma, Brushfield spots and all kinds of dark and light areas in the iris."

Dr. Osher points out that using this approach requires a high-resolution camera and appropriate software. "I know of at least three companies that are doing this," he says. "The initial company I worked with was Micron Imaging. They were geared up to introduce this technology, but the recent flood in Nashville wiped them out. Haag Streit has just introduced a similar system, the Osher toric alignment system. [Dr. Osher has no financial interest.] And Tracey Technologies is developing a camera that can do the same thing, as well as import the information into the Hoya toric calculator. Using the iris in this way is a simple and accurate way to ensure accurate toric alignment.

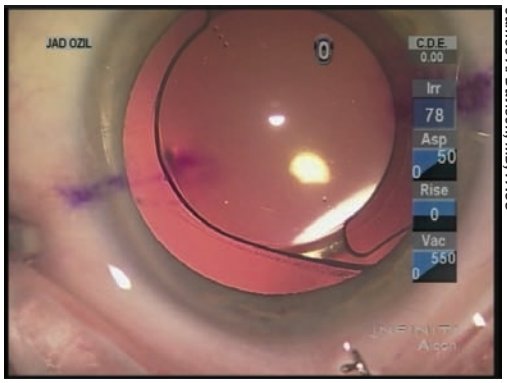
"The second approach is limbal registration," he continues. "This captures an image of the limbus when the patient is upright and looking into the distance, and then allows you to overlay the captured image onto the live image in the OR. The software superimposes them and tells you exactly where to rotate the lens to have it be accurately oriented."

Dr. Osher says at least three companies are currently offering this technology. "One company is SMI, recently purchased by Alcon," he says. "I've had their system for three or four years, and it works very well. The patient is registered in the preop area. The registration recognizes 250 points in the image, including vascular landmarks and some peripheral iris points, and lines them up. You can inject the image into the microscope, or have a separate dedicated monitor which allows you to see how much to rotate the lens. The SMI technology also lets you see the size of the capsulorhexis

and determine where you'd like to make the incision, and it helps with centering the lens—especially important with a multifocal lens. Zeiss and TruVision also offer limbal registration technology."

Intraoperative Aberrometry

Dr. Osher says the third and most sophisticated option is intraoperative visual field aberrometry. "Most surgeons are aware of WaveTec's ORA system, which uses Talbot-Moiré-based interferometry technology," notes Dr. Osher. "That system has been the leader in intraoperative wavefront aberrometry. However, that is a static system; you take a picture, then rotate the IOL.



James A. Davison, MD, FACS

Just before reorientation three weeks after the initial surgery, this toric IOL has rotated almost 90 degrees from its original position (re-marked in ink). The anterior capsulotomy was too large, leaving the anterior capsule just touching the optic edge on the top, bottom, and left; its edge is beyond the optic on the right. Early fusion of the anterior and posterior capsules can be seen on the bottom just peripheral to the optic and haptic edges.

"I've worked with a newer system from Clarity Medical Systems, called Holos IntraOp," he continues. "Holos does real-time dynamic wavefront aberrometry scanning. You don't need any preoperative information. It literally measures the eye's toricity on the table, and as you rotate the lens, you see what effect the rotation has in real time. When the image indicates that cylinder is no longer present, you've neutralized all of the astigmatism and you stop rotating. It's accurate to within one degree. And it has other advantages, such as confirming emmetropia, which is very important. So far, the Clarity system is still not available, although a prototype was shown at the 2012 American Academy of Ophthalmology meeting in Chicago.

"Unfortunately, right now there's not a huge incentive for surgeons to invest in this kind of new technology to address astigmatism," he adds. "Because let's face it: If you take the cataract out, the patient should see better. If you also correct the preop near- or far-sightedness, the patient will see better than ever. If you then correct the astigmatism, the patient will see even better still, but that's the icing on the cake. Nevertheless, cylinder is a component of the pseudophakic refractive error and, if the holy grail is emmetropia, we should attempt to reduce or eliminate preexisting astigmatism, period."

Of course, not everyone is sold on the value of the intraoperative approach—at least in its current (static) form. "If you're basing your orientation on really accurate readings, I don't think an aberrometer will change the axis that much," says Dr. Davison. "It's the same for the spherical component. The data I've seen says that about 6 percent of intraoperative aberrometry patients still end up with 0.75 D or more or spherical equivalent residual refractive error after surgery. Without using aberrometers, we have 7 percent of our patients with 0.75 D or more of residual spherical equivalent refractive error after surgery. Of course, that technology will get better. If we can get it down to 1 percent of patients with that much residual spherical equivalent refractive error, that would be a better argument for adopting the technology."

Dr. Osher adds that a simpler tool like the ThermoDot Marker is valuable, even if you have access to advanced technology such as the ORA or Holos system, or iris or limbal registration. "Relying solely on one technology, no matter how advanced, is like flying with one propeller," he says. "I'm OK with that, but I still like to have my marks as a fallback. For example, I had a case recently in which the ink mark that my nurses always put on at 6:00 diffused; I couldn't tell where the original mark had been. At the same time, I couldn't use limbal registration because the anesthetic that was given dissected under and raised the conjunctiva, totally distorting the anatomy. Having an indelible mark is an important safeguard; if something goes wrong, you still have a way to proceed. When I'm orienting a toric lens, I'm not willing to depend on one technology, any more than I'm willing to depend on a single preop measurement of K."

Measuring & Marking Pearls

These strategies can help maximize toric outcomes:

• ***Use multiple measurements when getting the K value.*** "I conducted a large study with Dr. Andrew Browne," says Dr. Osher. "We discovered that every technology will yield a certain number of outliers. In my office we get a manual K and then measure keratometry with five other technologies. (I know that no one else is that obsessive about it.) Any given technology will produce outliers; so the more measurements you have, the more likely it is that this 'melding' strategy will produce accurate outcomes."

"At least one of the devices you use should be a topographer," adds Dr. Koch. "We use the Lenstar, IOLMaster and two topographers. With the topographers we look at the overall appearance of the map, independent

of the SimK, to see where the image shows the overall astigmatism to be. That should match what we've found with the other measurements. If not, we know there's a problem."

• ***Look at the average topographer measurements over the central 3 or 4 mm.*** "In most devices, SimK represents just a few spots at the 3-mm zone," Dr. Koch points out. "The average measurement of astigmatism over the entire central 3 or 4 mm is a more valuable number. Ideally, it should be in agreement with the Lenstar or IOLMaster reading."

• ***Consider what the refraction shows.*** "If it's a good refraction and the patient has good enough vision that it's meaningful, it often gives me some clues about the against-the-rule astigmatism that may be present on the posterior corneal surface," says Dr. Koch.

• ***Check all of the data points.*** "There will always be mystery cases," notes Dr. Koch. "I saw a patient who had 2 D of with-the-rule astigmatism in her cornea, and 1 D of against-the-rule in her glasses. I didn't do any astigmatism correction during her cataract surgery, and she ended up 20/20 uncorrected. She had some posterior corneal astigmatism, and she may have had some lenticular astigmatism as well, to create that big a disparity between the cornea and the lens. So looking at all of the data points is important."

• ***Proceed with caution if the patient has anterior basement corneal dystrophy.*** "These eyes can produce an unusual topographical map," notes Dr. Davison. "Sometimes it's hard to know exactly where to orient the lens. The other thing is, if the patient's corneal epithelium changes from day to day, sometimes the patient gets better performance on one day than another day. Their expectations may be so high that they'll be disappointed by fluctuating vision, which, of course, they would also have with a

non-toric IOL."

• ***Don't wait to record the results of your measurements.*** "Enter the results of your testing into the record right away to avoid mistakes," says Dr. Davison. "We designed a template for our EHR system for this purpose. While we're in the room with the patient and getting the Pentacam, IOLMaster and Lenstar readings, we immediately enter them into our template. The nurse and I both double-check the numbers, and they're checked again later, before surgery."

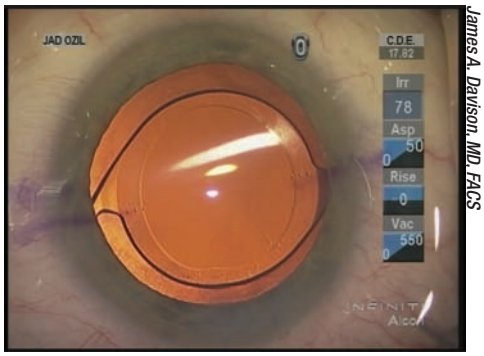
• ***Base the cylinder correction on the corneal astigmatism, not the refractive astigmatism.*** "When the patient has cataract surgery, any amount of lenticular astigmatism that was there will be removed," Dr. Jacob points out. "Only the corneal astigmatism will be left behind, so that's the thing you should treat."

• ***Know your specific surgeon-induced astigmatism factor.*** "It's important to personalize your SIA, so you can put this number into the toric IOL calculator," says Dr. Jacob.

• ***Be wary of leaving the patient with against-the-rule astigmatism.*** "Patients generally tolerate with-the-rule astigmatism better than against-the-rule astigmatism," says Dr. Jacob. "So, with with-the-rule you have to be very careful about how much you're treating. Overcorrecting it can create some against-the-rule astigmatism, which the patient won't tolerate."

• ***Always check your marks after you make them.*** "Don't assume that your marks are right at 180 or 90 degrees," says Dr. Koch.

• ***Make sure the patient is marked before using a retrobulbar block.*** "Make sure everyone in the OR knows that the patient is receiving a toric IOL so that blocking is not done until after the axis has been marked," says Dr. Jacob. "If the patient is blocked before you're able to mark the axis, you won't be able to mark it accurately."



James A. Davison, MD, FACS

An approximately 4.6-mm diameter circular capsulorhexis created with a femtosecond laser has resulted in a nearly ideal anterior capsule/optic overlap of approximately 0.7 mm on the right and left, and 0.6 mm on the top and bottom.

• ***If you're using ink marks, alert the person prepping the patient to avoid excessive washing of the cornea.*** "Loss of the ink marks can be a problem, and excessive washing of the cornea is likely to cause that," Dr. Jacob notes.

Pearls for the OR

• ***Bring the toric axis printout with you into the OR and turn it upside down.*** "All the toric IOL manufacturers give you a printout from calculators that are available on line," Dr. Jacob points out. "The printout shows the intended axis of placement and the site for the clear corneal incision, in order to take your surgically induced astigmatism into account. Turning the printout upside down makes these marks match the view you have of the eye, which helps to avoid mistakes in alignment."

• ***When the eye is very long, consider making the Descemet's entry portion of the incision a little more central so that its total length is 2 mm.*** "This makes it easier to avoid overinflating the eye, so it seals nicely with normal IOP," says Dr. Davison.

• ***Consider creating a slightly smaller capsulorhexis.*** "If you make it 5 mm, that helps to prevent the edge of the optic from popping out of the bag, or the IOL rotating excessively," says Dr. Jacob. "It's good to have overlap of the capsulorhexis all around the optic."

• ***Don't base your capsulotomy size on the size of the pupil.*** "When working on a bigger eye, surgeons have a tendency to make a bigger capsulotomy," notes Dr. Davison. "But if the capsulotomy is too big, the lens is more likely to rotate after surgery."

Dr. Davison cites a study he did with New Mexico surgeon Art Weinstein, MD. "We showed that about 3.4 percent of the lenses between 6 and 10.5 D actually rotated enough after surgery that they had to be reoriented," he says. "From 11 to 15.5 D it was 1.4 percent; for 16 D to 20.5 it was about 0.5 percent. No eyes over 20.5 D had to be reoriented. It appears that part of the reason for this might be that there's no real template to use to get the right size capsulorhexis, so you just make it to fit inside the pupil. That's a problem, especially in big eyes. The bigger capsulorhexis allows the toric lens to rotate more easily.

"The problem is, if you deliberately try to make the capsulotomy smaller, you might make it smaller than 4.6 mm," he says. "Then you'll have a higher tendency for capsular contraction and anterior capsule phymosis, which you don't want either. So I think there's a sweet spot there for the high myope; you don't want the diameter smaller or bigger than 4.6 mm."

Dr. Davison notes that one way around this is to make the capsulotomy with a femtosecond laser. *(See photo, above.)* "We've had a femto cataract laser since spring," he notes. "If you make it part of your astigmatism package, you can make the capsulotomy exactly 4.6 mm, so it embraces the toric IOL perfectly. That should minimize the likelihood that you'll have to reorient the lens postop.

"The most obvious way to see whether your capsulorhexis is the right

size is to check it against the three little dots on the toric lens," he adds. "The three little dots on the toric lens are at 0.2, 0.45 and 0.7 mm from the optic edge. So if the capsulorhexis is 4.6 mm—what I think is the perfect size for a high myope—the internal little dot on the toric lens should touch the edge of the capsulotomy when you're done. I used to have to reorient 1.2 percent of these cases postop. Since paying attention to these details, my rate has dropped to 0.6 percent."

• ***Expect the lens to rotate a little when you remove the viscoelastic.*** "When rotating the lens, stop about 10 to 30 degrees short of the intended axis," says Dr. Jacobs. "While removing the viscoelastic the IOL will rotate a little bit more. If you put it exactly on the mark before removing the viscoelastic, it's possible that the IOL will move during the viscoelastic removal, causing you to overshoot the intended axis. Trying to rotate it back in the opposite direction, counter-clockwise, doesn't work because it doesn't move well in that direction. If you overshoot, you'll have to rotate 180 degrees."

• ***Be especially careful when the lens sits vertically, standing on its inferior haptic.*** "A vertically oriented lens is like standing a pencil straight up on your desk," notes Dr. Davison. "It wants to tip over. If you stand a lens up inside the eye to manage with-the-rule astigmatism, it eventually wants to be oriented not at 90 but 180 degrees. That's what happens to some high myopes; the lens just falls off-axis, like a pencil tipping over. So it's important to do everything you can to prevent the lens from rotating in this situation." Dr. Davison adds that in his study of postop lens rotation (mentioned above), almost all of the cases that required reorientation were with-the-rule astigmatism where the IOL was oriented vertically.

• ***When using iris retractors, align the lens before removing the retractors.*** "When you have a patient with a small pupil, you may have to use iris retractors to make the pupil bigger," notes Dr. Davison. "The usual order toward the end of the surgery is to take the iris retractors out and then take the viscoelastic out, but if you do that in this situation, the pupil comes down and you can't align the lens. So, you have to align it before you take iris retractors out. Go ahead and remove the viscoelastic, do some stromal hydration to the incision, then do your adjusting maneuvers so the lens lines up. Then you can take the retractors out.

"When you're doing this you might lose a little bit of anterior chamber

depth," he adds, "because you still have some leakage around where the iris retractors are. If so, you may have to reinflate the eye a little bit."

• ***Make sure you do a thorough viscoelastic removal.*** "One of the major causes of postoperative IOL rotation is retained viscoelastic within the bag," notes Dr. Jacob, "So the surgeon should gently lift the edge of the IOL optic with the tip of the I/A probe and remove the viscoelastic left behind the optic of the IOL."

• ***Once you've removed most of the viscoelastic, gently tap down on the lens to help it adhere to the posterior capsule.*** "The tacky nature of the lens surface helps it adhere to the posterior capsule, preventing further rotation," says Dr. Jacob.

• ***Don't overinflate the bag.*** "At the end of surgery most surgeons instill balanced salt solution into the anterior chamber to maintain IOP," notes Dr. Jacob. "But if you overinflate the anterior chamber with BSS, the BSS goes behind the IOL into the space between the IOL optic and the posterior capsule, which can increase the tendency for the IOL to rotate."

• ***Consider putting air rather than BSS into the anterior chamber at the end of surgery.*** Dr. Jacob prefers this option. "The air forms a bubble that pushes the optic of the IOL backward, helping to prevent rotation," she explains. "It also prevents overinflation of the bag because it doesn't go behind the optic, unlike BSS. In addition, it acts as an internal seal for the corneal incision and decreases the chances of wound leak, endophthalmitis or a shallow anterior chamber. The trade-off is that the patient won't have good vision immediately, but I believe the benefits are worth the trade-off."

• ***If you need to reorient a lens, try to wait about three weeks.*** "Sometimes that's hard, because patients may have a lot of cylinder for those three weeks," says Dr. Davison. "But waiting allows the early capsule fibrosis and shrinkage to start, making things a little contracted and a little bit sticky. The capsular bag starts to adhere to the IOL haptics. Then, when you go in and rotate it again, it's more likely to stay where it's supposed to.

"There are a lot of ways to do the rotation at that point," he continues. "I've heard of people trying to do it at the slit lamp, but I think that's risky. I go back to surgery and use the original incision. I put Provisc (sodium hyaluronate 1%) on the anterior surface of the lens and fill the anterior

(continued on page 50)

How to Put an IOL in Its Place

Walter Bethke, Managing Editor

Experienced implant surgeons share their best techniques for refixating malpositioned lenses.

Having an intraocular lens decenter or drop into the anterior vitreous, days or years after cataract surgery, is an infrequent but onerous complication for surgeons to deal with. There are many options and plans of attack to consider, including the possibility of performing a limited vitrectomy. In this article, expert implant surgeons discuss the techniques that work best for them when they decide that a displaced IOL is worth salvaging.

Milder Malpositions

When approaching relatively mildly displaced intraocular lenses, surgeons often break them down into several categories:

• ***Decentered lens in the capsule.*** Here, the bag is in place but the lens is malpositioned inside it. "These are usually plate haptic lenses, or lenses in which there is a malformation of the haptic or a missing haptic," explains Richard Hoffman, MD, of Eugene, Ore. "For this scenario, I'll usually viscodissect the bag open and rotate the lens 90 degrees. Usually, at that point the lens will stay centered, especially if it's a plate lens. If it doesn't stay centered, you can capture the optic through the anterior rhexis and center it. However, I've never had to do that when the lens is in the bag and decentered."

• ***Lens partially out of the capsule.*** In this scenario, one haptic is in the capsular bag while the other is outside of it. "Usually, these lenses have to be dealt with because the haptic that's out of the bag is rubbing against the iris and causing problems," Dr. Hoffman says. "However, the approach for this is similar to that for a decentered lens in the capsule: You can usually get the bag viscodissected open and then reposition the lens within the bag."

• ***Decentered sulcus lens.*** In some cases, the original implant surgeon needed to implant the lens in the sulcus, following a complication such as a ruptured posterior capsule. However, in some cases these sulcus-fixated lenses can decenter later on. The fix for this gets more involved, surgeons say.

"In this situation, if the anterior capsule is intact, I'll prolapse the optic behind the anterior rhexis, which will center it," says Dr. Hoffman. "However, if there isn't an intact rhexis for doing that, I'll fixate the haptics to the iris with sutures."

Dr. Hoffman shares his iris suturing technique. "You can do it through two paracenteses," Dr. Hoffman explains. "First, create a paracentesis and inject

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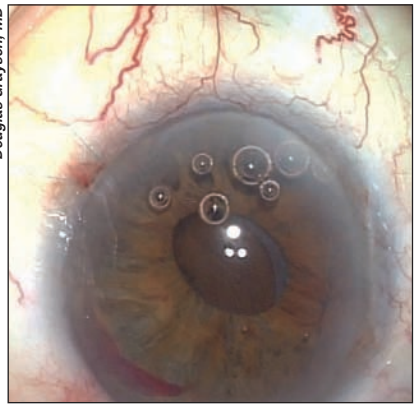
a small amount of viscoelastic in the anterior chamber and a small amount behind the optic. Then with a viscoelastic cannula you prolapse the optic forward in front of the iris, leaving the haptics behind the iris. Put some Miochol in the eye to constrict the iris behind the optic. Then, use either a 9-0 or 10-0 Prolene suture on a long curved needle and pass the needle through the paracentesis and then through the peripheral iris, incorporating the haptic." He secures the sutures with a Siepser knot.

Surgeons warn that the commonly used single-piece, hydrophobic acrylic IOLs shouldn't be refixated in the ciliary sulcus, due to the risk of uveitis glaucoma hyphema syndrome.[1]

• ***Partially malpositioned capsule and lens.*** Surgeons say long-term pseudoexfoliation is the most common reason for the capsule/lens complex to be displaced but that, in some mild cases, these malpositions can be remedied with a single suture. "One suture around a haptic through the sulcus, pulling the bag and lens in the direction from which it's falling will be enough to support it," says West Orange, N.J., surgeon Douglas Grayson. "In a mild decentration case, the eye tends to have intact zonules in the area that the capsule and lens are decentering toward. So the first thing I'll do is try to suture it through the haptic from the side that's most displaced. It's not always easy to do, because you don't necessarily want to blindly spear from inside to outside because you don't know what you might be hitting with the needle.

"I always like to spear from the outside in with a double-armed Prolene suture on an STC needle," Dr. Grayson adds, "and just try to get one suture above the haptic and one below it, come out of the clear corneal wound with the needles or right through peripheral cornea, use a Kuglen hook to externalize the Prolene through the paracentesis site, tie it down and secure it to the sclera in that manner." Dr. Grayson says he prefers this method to iris fixation. "In my experience, iris fixation often causes a secondary pigment dispersion glaucoma from chafing," he avers. "I've had one or two of these in which patients have developed intractable glaucoma and needed lens explantation, probably with a simultaneous glaucoma filtration procedure."



Douglas Grayson, MD

Suture fixation can be a good solution for sulcus lenses that shift out of position, but surgeons say to beware pigment dispersion glaucoma due to iris chafing.

Subluxated Lenses

In the more extreme cases of displacement, the bag/lens complex or the lens is in the anterior vitreous. This more complicated scenario will involve a limited vitrectomy and, if the surgeon feels the lens can be salvaged, fixating the lens in the eye. If the lens is sitting on the retina and a full vitrectomy is warranted, however, surgeons recommend the anterior segment surgeon get a retinal specialist involved to perform either the entire case or, at least, the vitrectomy portion.

For complicated dislocations, two of the newest methods for fixating the lens that have emerged over the past several years are the scleral pocket fixation of the sutures, developed by Dr. Hoffman, and fixating the haptics beneath scleral flaps using fibrin glue, described by Amar Agarwal, MD, of Chennai, India.

Before surgeons can use either of those techniques for the subluxed lens, however, a limited vitrectomy will need to be performed. Surgeons also emphasize the necessity of a meticulous retinal exam before and after the limited vitrectomy/lens refixation procedure in these patients, in order to catch any tears or other pathology. Here is how to proceed with the case.

• ***Pearls for anterior vitrectomy.*** Cincinnati Eye Institute retinal specialist Christopher Riemann says when the vitreous gets involved, anterior segment surgeons should ask themselves who is the best person or persons to fix it—themselves, the retina specialist or a combination? "This a bigger question than one might think," he says. "Because there are a lot of surgical videos out there with very involved techniques. That doesn't necessarily mean these are the right ways to take care of these patients.

"If the lens is decentered in the capsular complex and the eye has already had a complete vitrectomy, then I don't have a problem with any anterior segment surgeon maneuvering the lens around and getting it where it needs to be," Dr. Riemann continues. "But issues arise when there's vitreous present and a limited vitrectomy is called for. Ask, 'How limited is it going to be?' " He has three conditions for what he calls a limited vitrectomy: "If there are a couple strands of vitreous in front and the surgeon will just be cleaning out the front and blowing the rest back with viscoelastic; if the lens is already in the iris plane or ciliary sulcus plane; or if we don't think it's luxed posteriorly where its haptics are caught in the vitreous base—in which any tugging on the haptics will result in traction on the retina—then I think it's fine for an anterior segment surgeon to perform the surgery," he says.

Dr. Riemann believes there are two acceptable ways to perform the anterior vitrectomy. "First, surgeons can use bimanual anterior segment infusion and anterior segment vitrectomy port entry, both through two paracenteses," he says. "This is much better than a coaxial, single-wound approach, which is probably the worst technique to use. This is because with the two-paracenteses technique, the vector of the irrigating fluid isn't directly into the vitreous cavity as it is with coaxial. With two paracenteses, you can do a very nice job of cleaning up a little bit of vitreous in the anterior chamber. If you have to go behind the lens though, you have to kind of go fishing for vitreous, and that, in my mind, can be a little problematic."

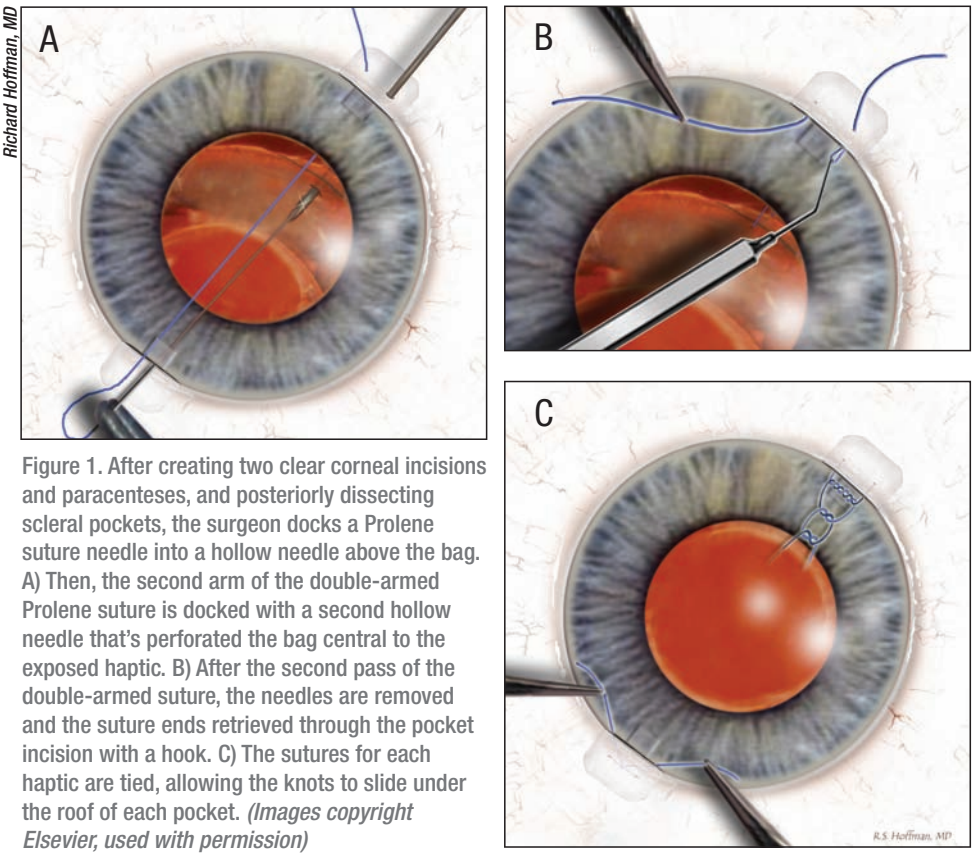


Figure 1. After creating two clear corneal incisions and paracenteses, and posteriorly dissecting scleral pockets, the surgeon docks a Prolene suture needle into a hollow needle above the bag. A) Then, the second arm of the double-armed Prolene suture is docked with a second hollow needle that's perforated the bag central to the exposed haptic. B) After the second pass of the double-armed suture, the needles are removed and the suture ends retrieved through the pocket incision with a hook. C) The sutures for each haptic are tied, allowing the knots to slide under the roof of each pocket. *(Images copyright Elsevier, used with permission)*

For the safest, most effective anterior vitrectomy, Dr. Riemann thinks surgeons should be working through the pars plana. "I'm a little biased as a retina surgeon, but I think the very best way is with an anterior infusion through a paracentesis and a single pars plana port," he says. "That is absolutely the right way to do it, because the vector of fluid flow is from front to back in a way that doesn't hydrate the vitreous. And, the default position is everything falls back to the cutter and puts the cutter where you need it, which is kind of right behind the IOL in that very anterior vitreous space."

To get the best, safest results, Dr. Riemann recommends a few things. "First, use trocar-based ports," he says. "They are clearly safer than non-trocar sclerotomies. When you're using a trocar, the innermost point of the wound is often 3 to 4 mm inside the globe. In this way, you've moved away from the vitreous base, thereby reducing vitreous traction.

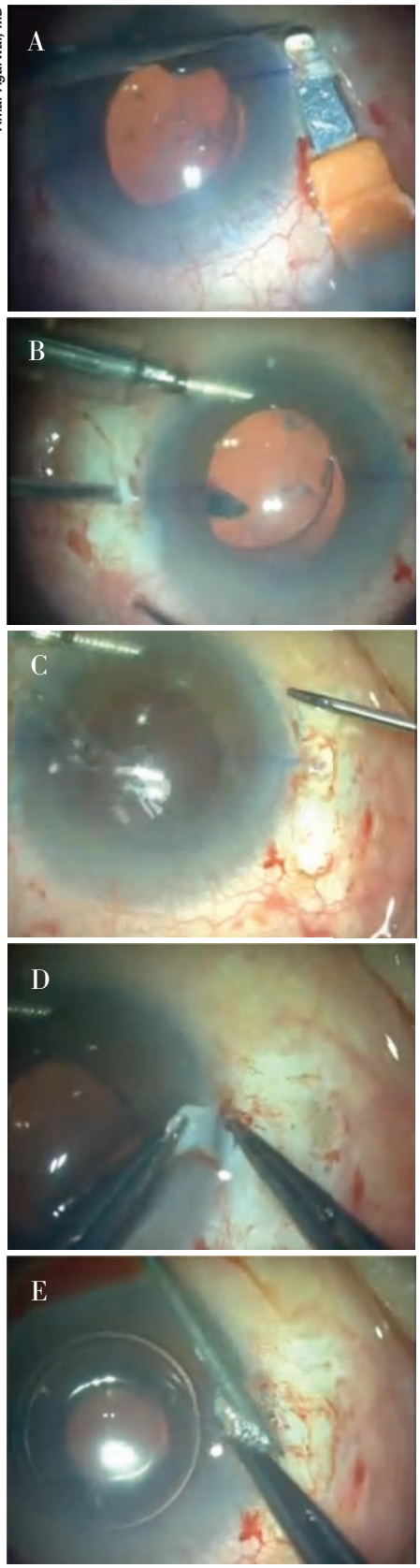
"Second, I think it's very important to use the smallest gauge vitrectomy system possible," Dr. Riemann continues. "There's no reason for an anterior segment surgeon to use a 20-ga. or 19-ga. vitreous probe through a sclerotomy, when he or she could be using a 23-, 25-, or 27-ga. probe through an appropriately sized trocar. Not only do the smaller gauges seal better, but their risk of iatrogenic retinal breaks is much lower when used with the trocar entry port.

"Third, the highest possible cut rate is always better than the lowest, and very conservative vacuum settings should be used, because the more you pull, the more likely you are to create retinal breaks," Dr. Riemann continues. "A good starting point for 20-ga. surgery would be a vacuum of 100 to 150 mmHg; for 23-ga. it's 150 to 250; for 25-ga. it's 300 to 400; and for 27-ga. it's 400 to 500 mmHg." Additionally, Dr. Riemann says that an injection of diluted triamcinolone before the vitrectomy will help mark the vitreous strands to make it easier to remove them.

For whichever suture technique follows, Dr. Riemann doesn't feel 10-0 Prolene is appropriate. "10-0 Prolene has a high breakage rate after about 10 to 12 years," he says. "After which you're back in the eye trying to suture refixate. 9-0 Prolene is the minimum size. Another option is Gore-Tex, which isn't actually approved for ophthalmic use, but has worked well for myself and many of my partners."

• ***Scleral pocket technique.*** This technique has found favor with surgeons because it avoids the need for conjunctival dissection and scleral cautery that are used in previous techniques. It also has the potential to

Amar Agarwal, MD



leave a healthy bit of sclera above the suture, to prevent erosion. Dr. Hoffman explains the technique:

"Rather than cutting down the conjunctiva and creating two rectangular flaps in the sclera, I'm creating two pockets in the sclera starting in the cornea and then dissecting posteriorly by about 3 mm," he says. "The way to start that is to place two grooved incisions at the limbus in clear cornea, 180 degrees away from each other in a meridian that allows you to fixate the haptics to the sclera. If you just try to fixate the capsular bag to the sclera, it doesn't work. If a patient has a [capsular tension ring] in the bag, that's ideal, because you can basically suture the bag anywhere for 360 degrees using the CTR as a haptic. If they don't have a CTR in place, then you have suture the haptics, and if the haptics are oriented in the right place, then it's fine. But sometimes they're oriented 90 degrees away from where you'd like them to be oriented and it can make it a bit more challenging.

"You make a 350-µm deep groove in a meridian that allows you to fixate the haptic to the sclera," Dr. Hoffman continues. "Then you dissect that groove posteriorly in the plane of the sclera, going back about 3 mm. This creates the scleral pockets. Then you make a paracentesis in front of each pocket, and pass a double-armed, 9-0 Prolene suture through the paracentesis and dock it into a 27-ga. needle that's passed through the full thickness of the globe corresponding to where that pocket is. *(See Figure 1, p. 31)* The first double-armed suture would go in front of the bag, or through it, and the second one would go the other way, so that one passes through the bag and the other passes in front of it. The pass going through the bag is really going behind the haptic, so that when you pull that suture into the eye, it's looped around the IOL haptic. So you pass the 27-ga. needle about 2 mm posterior to the surgical limbus, which is perhaps 3 mm from where the conjunctival insertion is, and then you pass the second 27-ga. needle right next to that—or just in front of it—but I usually just do it next to it so that the suture's going through the bag and in front of the bag and out through the full thickness of the globe. If you can't visualize the capsular bag equator, you can put a hook in through the paracentesis that's just in front of the pocket while you're passing the needles from the opposite paracentesis and docking the sutures into the 27-ga. needles.

"Then, you take the needles off the sutures," Dr. Hoffman explains, "go into the pocket with a Sinskey hook and pull both ends out so that they're externalized through the opening in the scleral pocket, and then tighten and tie those. That allows the knot to slide under the protective roof of the scleral pocket so that it's less likely to erode through the sclera and the conjunctiva. You then do the same thing for the other side. The docking technique isn't my technique, and has been described by several other

Figure 2. A) In the Agarwal glue fixation technique, the surgeon first creates two limbal-based scleral flaps 180 degrees apart. B) He then makes two straight sclerotomies with a 20-ga. needle 1 to 1.5 mm from the limbus under the flaps. This is followed by vitrectomy via pars plana or anterior route to remove all vitreous traction. Using forceps the surgeon lifts up the intraocular lens to the level of the sclerotomy sites. He withdraws the forceps (holding the haptic) from the sclerotomy site, externalizing the haptic. C) Then, with an assistant holding the first haptic, the surgeon externalizes the second. D) The surgeon tucks the tips of the haptics into a Scharioth intralamellar scleral tunnel created with a 26-ga. needle. The scleral flaps are closed with fibrin glue (E), followed by a glue closure of the conjunctiva.

surgeons, including Javier Moreno-Montañés, MD; Ike Ahmed, MD; and Alan Crandall, MD. My contribution to this is the scleral pockets—which have the advantage that you don't have to dissect the conjunctiva. Therefore, I believe that the tissue is healthier and is much less likely to erode over the underlying knot that's created." For a video of the technique as performed by Los Angeles surgeon Sam Masket, visit https://www.youtube.com/watch?v=McwNhj-PMmo.

• ***Glued haptic technique.*** Dr. Agarwal says adding glue to the scleral incarceration of the haptics results in a more stable lens. (The technique of scleral incarceration, but without glue, was originally described by Recklinghausen, Germany's Gábor Scharioth, MD, PhD.) "There is no pseudophacodonesis as might occur if the haptics were just sutured," Dr. Agarwal says. "Since the haptics are glued under scleral flaps rather than sutured, the lens doesn't move postop. As a result, the quality of vision is very good. The only instance in which I can't use the glue technique is if it's a single-piece, foldable IOL. In that case, I'll explant the lens and refixate a new lens in the eye."

For a subluxed IOL, Dr. Agarwal says the technique first involves creating two partial thickness, limbal-based scleral flaps 180 degrees apart. *(See Figure 2, p. 32)* Then, the surgeon performs the anterior vitrectomy. He then uses forceps to bring the lens up to the level of the sclerotomy sites and externalizes one of the haptics by withdrawing it through one of the sclerotomies. As an assistant grasps the end of the externalized haptic with forceps, the surgeon uses another pair of forceps to pull the other haptic through the opposite sclerotomy. He then tucks the ends of the haptics into a Scharioth intralamellar tunnel he creates with a 26-ga. needle, right at the spot of externalization. The surgeon then closes the scleral flaps over the externalized haptics with fibrin glue (Tisseel, Baxter).

In this technique, Dr. Agarwal says it's crucial to grab the tip of the trailing haptic when externalizing it, since grasping the middle of the haptic and trying to pull it out of the eye could break it. To make this easier, Dr. Agarwal developed the "handshake" technique. In this technique, the surgeon flexes the second haptic into the anterior chamber and into the grip of the second forceps introduced through the other sclerotomy. He then passes the haptic from one forceps to the other until the tip is properly grasped for externalization.

In terms of complications, Dr. Agarwal recently completed a study of eyes done with the glued-IOL technique with an average follow-up of 17 months. In 191 foldable lenses, the most common complication was optic capture (5.7 percent). IOL decentration occurred in 2.6 percent of eyes. Haptic-related complications in the late postop period were haptic displacement (2 percent), tip extrusion (0.5 percent) and subconjunctival haptic (1.5 percent).[2]

"By and large, these eyes are very quiet postop," says Dr. Agarwal. "This is because the lens doesn't move. Because of that, the vitreous and other structures remain quiet when compared to an iris-sutured IOL, a scleral sutured lens or an anterior chamber IOL." For a video of the technique, visit https://www.youtube.com/watch?v=UYZkHPojJ7Y.

• ***Snyder half-hitch suture.*** Dr. Grayson says working with externalizing the haptics and creating channels can be technically complex, and is not for everyone. "I do a lot of precision surgery because I'm primarily a glaucoma specialist, so I'm used to suturing and manipulating in the eye, and I still find some of these maneuvers difficult to do," he says. Instead, he's had success with rotational knots such as those used in a half-hitch suture technique described by Cincinnati Eye Institute's Michael Snyder, MD. Dr. Riemann, who works with Dr. Snyder, also uses the technique.

"You make two beveled sclerotomies into the ciliary sulcus that are quite some distance apart," Dr. Riemann explains. "Personally, I use vitrectomy trocars instead of sclerotomies. You then place a half-hitch suture around the haptic and move in a radial direction from the knot, which creates tension that tends to pull the lens parallel. You come out through the sclerotomies, or the trocars, then tie the knot and rotate the lens in such a way that it is rotated as far counterclockwise as possible, then tie the knot on the outside of the eye over the most counter-clockwise sclerotomy.

Once the knot is tied and secured, you can rotate the entire knot into the eye through the sclerotomy. In that way, you're actually sliding the haptic in a clockwise fashion—actually slightly rotating the lens clockwise—so not only does that make the suture knot disappear on the inside of the eye, completely burying it, it also lets you adjust the centration of the lens by rotating each knot." For a video of the technique, visit revophth.com/Snyder_Suture.

Whichever technique you choose to use for managing a malpositioned lens, Dr. Grayson says that education and practice are key. "These are complex procedures, and are almost a dying art," he says. "I'm not sure how many times during a residency a resident is taught these suture techniques, because there is no suturing left in cataract surgery, but you need to get the feel of regularly handling sutures." REVIEW

1. LeBoyer RM, Werner L, Snyder ME. Acute haptic-induced ciliary sulcus irritation associated with single-piece AcrySof intraocular lenses. J Cataract Refract Surg 2005;31:7:1421-7.
2. In press: Kumar DA, Agarwal A. Glued intraocular lens: A major review on surgical technique and results. Curr Opin Ophthalmol 2012;23.

Surgeon Opinions on Implants and Explants

Walter Bethke, Managing Editor

Surgeons like presbyopic lenses, but see room for improvement.

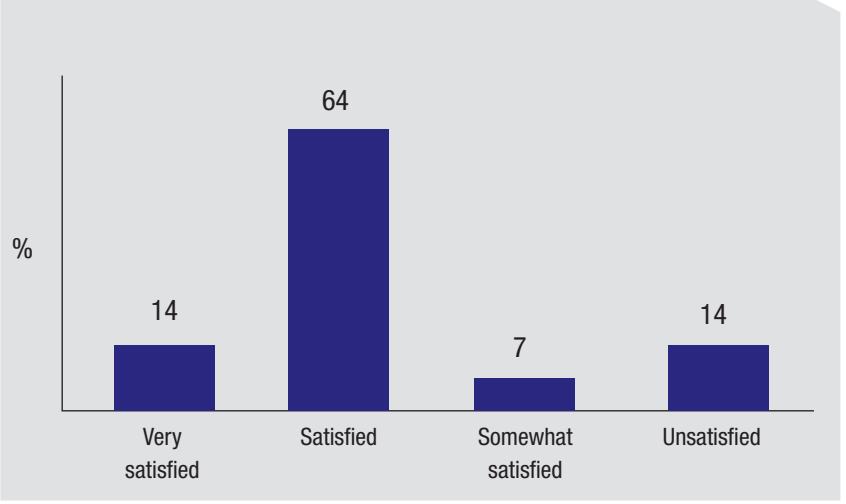
Regarding the newer technology intraocular lenses available to ophthalmologists, respondents to our latest National Panel questionnaire say they implant a modest number each month, and are very satisfied with their performance. When it comes to lens features, surgeons value asphericity, or neutral asphericity, the highest. However, it's taking surgeons a while to embrace phakic IOL technology, and some still have issues with the performance of those lenses.

These are some of the results from this month's survey on intraocular lenses. This month, 23 surgeons (4.6 percent) of our 500-physician panel responded. See how your preferred practices compare with theirs.

Presbyopic Opinions

Fifty-six percent of respondents implant multifocal, diffractive or accommodating IOLs. In terms of presbyopic lens performance, 64 percent say they are satisfied, 14 percent are very satisfied, 7 percent are somewhat satisfied and 14 percent are unsatisfied. On the survey, 43 percent of surgeons implant the

Surgeon Satisfaction with Presbyopic IOLs



This article has no commercial sponsorship.

ReSTOR +3 D lens the most in their practices, 43 percent prefer the Tecnis multifocal and 14 percent use the Crystalens AO. Tecnis users implant an average of 10 per month with a charge of $2,479; ReSTOR users implant an average of six lenses per month with an average charge of $1,913; and Crystalens users report implanting an average of nine lenses per month, though they didn't share their average charge for them on the survey.

Robert Epstein, MD, of McHenry, Ill., often implants the ReSTOR. "I am satisfied—but not 'very' satisfied—with the ReSTOR," he says. "There are definitely patients with it who have awesome-looking eyes with no astigmatism but unsatisfactory vision. If there is any macular or dry-eye issue in the patient, then forget it; the multifocal lens results will be inadequate and you will wish you never agreed to put it in. The Lord did not necessarily align the center of the capsular bag with the center of the pupil, so surgeons should make sure that the two are aligned at the end of surgery for best results, but it may shift slightly or just not align that way. Definitely underpromise [to the patient]."

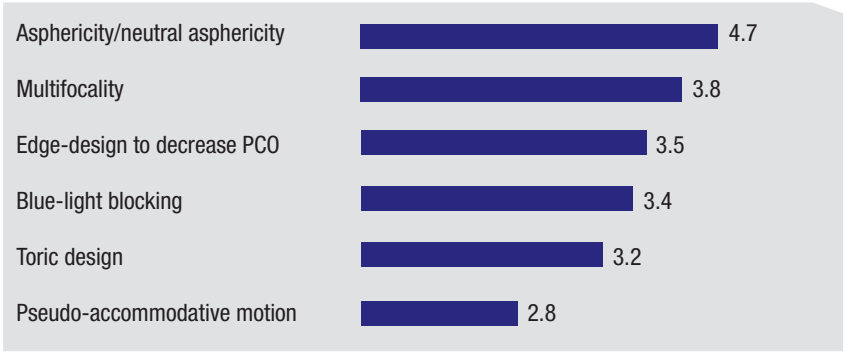
A surgeon from Florida says that though she is somewhat satisfied with the multifocal IOL that she uses, there is still room for improvement. "Multifocality is not the best solution for presbyopia," she says. Richard Erdey, MD, of Columbus, Ohio, says he's very satisfied with the Crystalens, but would like to see some tweaks: "The Crystalens is not a one-size-fits-all IOL," he says. "We perform UBM on all candidates and screen out those with short capsular bag diameters to avoid Z or U syndrome. B + L should offer a 0.5-mm smaller diameter option throughout the available power range."

Toric Performance

Panelists continue to be impressed with the

Surgeons Rate Toric IOL Performance

Surgeons Rank Features of IOLs



Surgeons ranked IOL attributes from 6 (most valuable) to 1 (least valuable). Shown here is the average score for each lens feature from the survey.

performance of toric IOLs, with 68 percent of the surgeons saying they implant them. Forty-seven percent rate toric IOL outcomes as excellent and another 47 percent say they're good. Only 6 percent say toric outcomes are only fair.

Miami ophthalmologist William Trattler says his toric outcomes have been "excellent," and Fort Myers, Fla., surgeon Mark Gorovoy says he thinks toric performance has been good, though he notes, "It's rare to hit 'zero' cylinder." Gerald Roper, MD, who rates toric performance as fair, says that in his experience, "Patient satisfaction is fair, and comparable to monofocal [lenses], but they are still spectacle-dependent at a high cost." Another surgeon from Florida says her experience with torics has been excellent, but adds, "I wish they didn't have glistenings."

IOL Materials and Features

Surgeons also weighed in on what they like about the lenses they use most, and the features, such as multifocality, asphericity or the presence of a toric correction, that they find most useful.

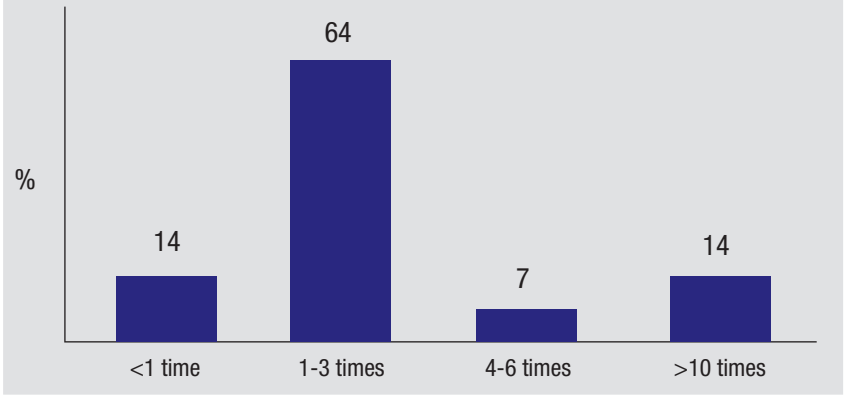
In terms of the lens they use most often, 43 percent of respondents say it's the Alcon SN60WF, 17 percent choose the Tecnis, 13 percent name the Bausch + Lomb SofPort AO, 8 percent prefer the Lenstec Softec HD, and the Rayner C-flex and Hoya iSymm/iSert each were chosen by 4 percent of panelists. Eight percent of the respondents chose "other."

In terms of the best material for IOL construction, acrylic was very popular among panelists, chosen by 80 percent of the surgeons. Ten percent like silicone, 5 percent chose collamer and another 5 percent prefer PMMA lenses.

"Acrylic folds easily and has good biocompatibility," says a surgeon from New York. A surgeon from New Jersey says, "The Alcon SN60WF is easy to use and a great option ... acrylic is biocompatible with silicone oil if it's ever needed for retinal work." A Tecnis fan from Maryland appreciates the lens for its "great centration, great optics, and the fact it's a single-piece lens," while a surgeon from Florida prefers the B + L SofPort AO for the same reasons: optics and centration. Dr. Trattler likes both the Tecnis and the Softec HD, saying, "Both IOLs provide excellent quality of vision, a very low incidence of negative dysphotopsia and, in general, no glistenings."

None of the surgeons report implanting the Implantable Miniature Telescope IOL (VisionCare, Saratoga, Calif.). "I very much like the idea," says Dr. Epstein. "I have brought up the idea to several patients and they were somewhat cool to it, though. I know the inventor, Isaac Lipschitz, MD, and he told me about a newer lens that only enlarges a part of the field of vision, rather than the entire field. I like that idea better."

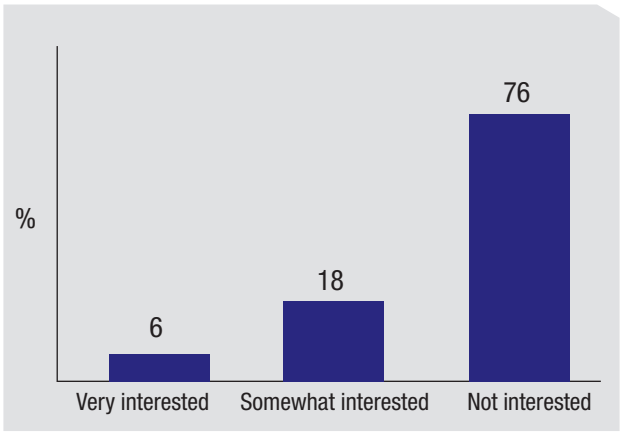
Surgeons' Annual Frequency of Suturing an IOL



Lens Complications

Though surgeons like their lenses for the most part, problems can and do occur from time to time. Fifty-three percent of our panelists say they have to re-enter the eye and suture one to three lenses per year, 12 percent have to suture refixate four to six lenses, and 6 percent have

Interest in Implanting Phakic IOLs



to suture more than 10 lenses. Twenty-nine percent, however, say they don't suture any lenses during the year (either because of no complications or because they just refer them to another surgeon for performance of the procedure).

Reasons for suturing include: loss of zonulocapsular integrity from trauma or pseudoexfoliation; dislocated lens/capsular complex; and planned scleral fixation in patients with significant zonular laxity. Dr. Epstein explains his suturing approach: "In these cases, I use intraocular forceps and do an intrascleral haptic burial technique that doesn't require sutures for the fixation," he says. "I used to perform suturing to the sclera into the sulcus. It's worthwhile to bury the suture with the knot intracorneally at the limbus, but the best way is with no sutures at all. The most annoying aspect of fastening the IOL to the sclera is dealing with sutures eroding through or around the scleral pocket and through the conjunctiva. I will sometimes operate on these cases with a vitreoretinal surgeon."

Surgeons also described the most common causes for explanting a lens and replacing it with a new one in the past year. These include:

- incorrect lens power;
- an unhappy multifocal IOL patient;
- luxation or malposition in general;
- haptic in the sulcus; and
- not achieving the targeted refraction in a premium lens patient.

Though many physicians and patients are satisfied with their patients' multifocal lens outcomes, some surgeons say it's almost inevitable that they will encounter an unhappy multifocal recipient at some point. Says Fort Myers' Dr. Gorovoy: "I see an unhappy multifocal IOL patient almost every week." REVIEW

Early Users Share the enVista Experience

Michelle Stephenson, Contributing Editor

Unlike other hydrophobic acrylic lenses, enVista's packaging technique provides glistening-free vision.

In mid-2012, the Food and Drug Administration approved the enVista hydrophobic acrylic IOL (Bausch + Lomb). This lens is the only FDA-approved lens with labeling that states, "no glistenings of any grade were reported for any subject at any visit in the clinical study."

"The FDA approved the enVista IOL as glistening-free following a 122-eye clinical trial involving six sites," says Peter Heiner, MD, from the Vision Eye Institute, Gold Coast, Australia. "All implanted lenses were evaluated by slit-lamp investigations and photography, and no glistenings were detected at any examination."

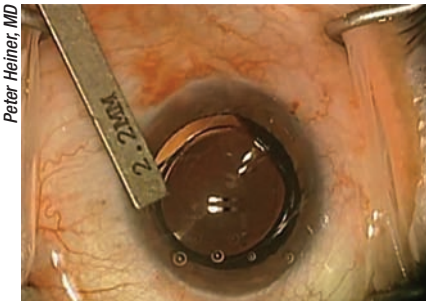
Glistenings

Glistenings are fluid-filled microvacuoles that form in the optic of the IOL in an aqueous environment. They have been found in many lens types, but have been found most frequently in hydrophobic acrylic IOLs, which are the most commonly implanted lens type in the United States and Australia.[1]

These glistenings form within the superficial layer of an IOL, potentially causing some of the light coming into the eye to be scattered. Glistenings not only present an aesthetic issue post-surgery for surgeons, but they can impact visual function. "We know that, if you grade glistenings on a scale of 1 to 4, anything over 2 causes a decrease in visual acuity of one line," says P. Dee Stephenson, MD, from Stephenson Eye Associates, Venice, Fla. "We know that glistenings affect vision, so why would you put a lens that has the potential for glistenings in a patient if you don't have to?" Dr. Stephenson was one of the first ophthalmologists to implant the enVista lens in the United States outside of the pilot study.

"Two of the functions of the natural lens of the eye are to provide refractive power and to remain clear," Dr. Heiner says. If the lens loses clarity, a cataract forms, and vision deteriorates. With the introduction of the enVista intraocular lens, we have a hydrophobic IOL that can provide refractive power and remain glistening-free."

He notes that many surgeons are concerned about the presence of glistenings and the possible deleterious effects on quality of vision. A study conducted at the John Moran Eye Center found that glistenings occur frequently in AcrySof IOLs, another hydrophobic acrylic IOL.[2] This study included 42 eyes that underwent phacoemulsification and implantation of an AcrySof IOL. Glistenings were



Peter Heiner, MD

The enVista can be inserted through a 2.2-mm incision.

graded at the slit-lamp from trace to 4+. The researchers found that all 42 of the IOLs had some degree of lenticular glistenings. They were graded as trace in 27 IOLs (64 percent), 1+ in five (12 percent), 2+ in five (12 percent), 3+ in three (7 percent), and 4+ in two (5 percent). In eyes with severe glistenings (2+ or higher), Snellen acuity was one-half line lower than in eyes with mild glistenings. The Brightness Acuity Tester score was just more than one-half line lower than the Snellen acuity. In eyes with glistenings graded above 2+, the difference was one full line. Of the 15 IOLs with glistenings graded higher than trace, 14 (93 percent) had been in the eye for more than one year. Researchers found no evidence that contrast sensitivity was affected by the glistenings.

Although it is uncommon, in some instances intraocular lenses have been explanted due to reduced quality of vision in the presence of dense glistenings. "With a tendency to operate on patients at an earlier age and for patients to live longer, it is comforting to implant a lens that will remain clear," Dr. Heiner says.

enVista avoids glistenings through pre-hydration and packing in 0.9% saline. The lens is 4 percent water, so it is in equilibrium with the environment in saline, which means that there is no water movement in and out of the IOL.

This lens is made of a proprietary highly cross-linked acrylic co-polymer. The enVista IOL is a single-piece lens with a modified-C haptic design. It has a 360° posterior square edge, 6-mm aspheric optic, and it is 12.5 mm long. The refractive index is 1.54. It is available in diopter ranges of 0 D to 9 D and 31 D to 34 D in 1-D increments and in diopter ranges of 10 D to 30 D in 0.5-D increments.

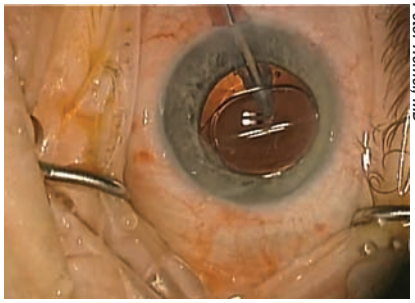
Additionally, the lens is very durable. According to Dr. Stephenson, some lenses can be damaged by the inserter or forceps, but the enVista IOL resists abrasions. "Therefore, the clarity of this lens is incredible, and it looks beautiful in the eye," she says. "The lens has a square edge and is aspheric. Aspheric lenses are aberration-free. They have uniform power from the center to the edge, so if they lens gets decentered or tilted, it will not induce any aberrations."

Postoperative Outcomes

Dr. Stephenson has implanted 50 lenses to date. Of these patients, 25 are six weeks or more postop. She uses the WaveTec Vision Ora system in the operating room to help improve her outcomes. All 25 patients' uncorrected visual acuity is 20/40 or better. All of those 25 patients are within 0.50 D of absolute predicted error, with the mean being 0.17 ±0.11. Seventy percent of those patients are within 0.25 D of absolute predicted error, with the mean being 0.17 ±0.11 as well. "These are better results than historical LASIK outcomes," she says.

A new coated inserter for the enVista lens was recently released. The new insertion system was designed to facilitate implantation through incisions as small as 2.2 mm, depending on surgeon technique. Using the previous inserter, the Accujet, Dr. Stephenson was working through a 2.4-mm incision. "With this new inserter, I think this lens will go easily through a 2.2-mm incision without any problem," she says.

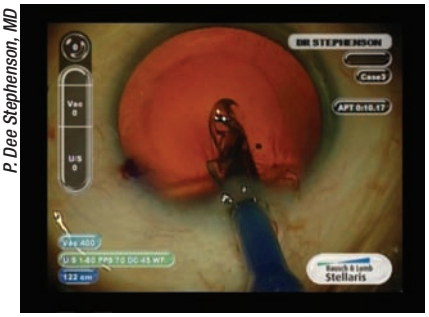
She also notes that the lens does not move once it is in the eye. "In fact, 91 percent move less than 5°, which is nothing," she says. "The lens unfolds slow and controlled. It is easy to rotate into the bag and remove the viscoelastic from behind the lens. She cites the features of the lens including a unique single-piece modified-C haptic design to provide rotational stability; fenestrated vaulted haptics with a 56° contact angle provide added stability; and it is vaulted, so the optic actually touches the posterior capsule.


Peter Heiner, MD

The viscoelastic can be easily removed from behind the optic during the controlled unfolding of the enVista IOL.

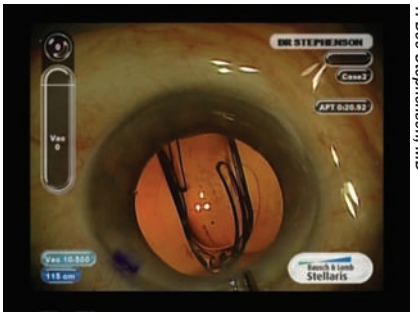
Dr. Heiner recently presented a poster at the AAO meeting detailing a study he conducted using the enVista lens *(Heiner P, Northcott M. Early clinical experience of a new hydrophobic intraocular lens. Presented at the 2012 annual meeting of the American Academy of Ophthalmology)*. The study included 46 consecutive eyes of 36 patients scheduled for cataract surgery with planned implantation of the enVista IOL. Patients' mean age was 74 years, with a range of 56 to 87 years. Cataract surgery was performed using the Stellaris phaco machine. Dr. Heiner used peribulbar anesthesia with intracameral supplementation. He used 2.2-mm temporal, clear cornea, three-stepped, self-sealing, square incisions and the microburst ultrasound setting. The 2.2-mm incision was not enlarged. The lens was placed using a Medicel Accuject injector system. Patients were given 1 mg intracameral cephazolin.

Preoperatively, 30 percent of eyes had uncorrected visual acuity of 20/40



P. Dee Stephenson, MD

The Accujet insertion system.



P. Dee Stephenson, MD

Controlled unfolding.

or better, and 5 percent had visual acuity of 20/30 or better. At two weeks after surgery, 98 percent had uncorrected visual acuity of 20/40 or better, 80 percent had uncorrected visual acuity of 20/30 or better, and 23 percent had visual acuity of 20/20 or better.

Three months postoperatively, 98 percent had uncorrected visual acuity of 20/40 or better; 82 percent had uncorrected visual acuity of 20/30 or better; and 45 percent had uncorrected visual acuity of 20/20 or better. Preoperatively, patients' mean uncorrected visual acuity logMAR was 0.606 ±0.368 (or 20/80). At two weeks postop, patients' mean uncorrected visual acuity logMAR was 0.115 ±0.129 (or 20/25-), and at three months postoperatively, patients' mean uncorrected visual acuity logMAR was 0.075 ±0.130 (or 20/25+).

Dr. Heiner also tested best-corrected visual acuity. Preoperatively, 87 percent of eyes had BCVA of 20/40 or better; 63 percent had BCVA of 20/30 or better; and 9 percent had BCVA of 20/20 or better. At two weeks after surgery, 100 percent had BCVA of 20/30 or better, and 80 percent were 20/20 or better. Three months postoperatively, 100 percent had BCVA of 20/30 or better, and 89 percent were 20/20 or better. Preoperatively, patients' mean BCVA logMAR was 0.179 ±0.135 (or 20/30). At two weeks postop, patients' mean BCVA logMAR was -0.023 ±0.05 (or 20/20+-); and at three months postoperatively, patients' mean BCVA logMAR was -0.037 ±0.054 (or 20/20+2).

At three months postoperatively, 100 percent had a spherical equivalent within ±0.75 D of target, and 80 percent had a spherical equivalent within ±0.50 D.

To date, Dr. Heiner has implanted 221 enVista IOLs. "I have found that this lens gives good results in terms of unaided and corrected vision," he says. "I routinely implant this lens through an unenlarged 2.2-mm temporal wound. This results in low surgically induced astigmatism of 0.4 D. To date, I have only needed to YAG eight eyes, which corresponds to a 3.6 percent rate."

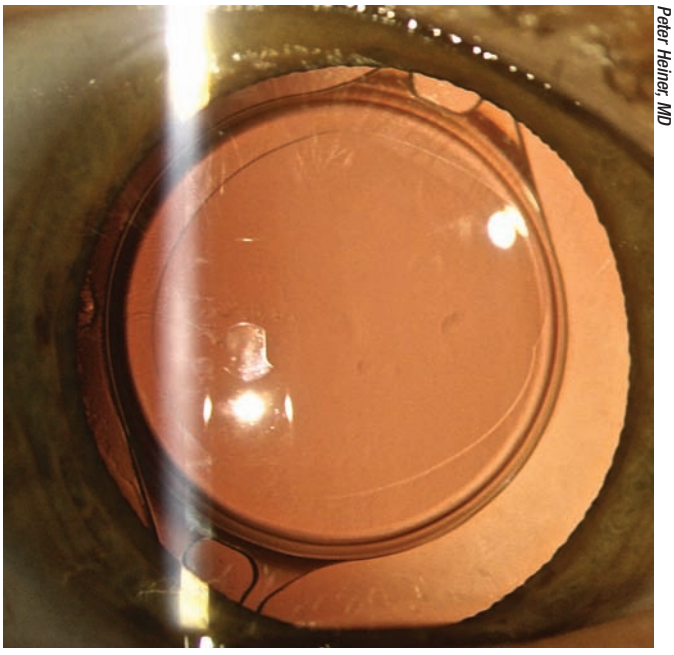
Interestingly, the enVista material has a relatively high glass transition temperature (Tg) of 28°C, which is responsible for the slow, controlled unfolding of the lens on implantation. According to Dr. Heiner, the lens centers well once it is inserted into the capsular bag.

"I have found the pace of the unfolding to be an advantage because it allows ample time for removing viscoelastic from behind the optic. I am able to insert the I/A tip between the optic and the posterior capsule and get all of the viscoelastic out before unfolding is complete," he says.

Also setting enVista apart from currently available IOLs is its combination of aspheric and aberration-free Advanced Optics (AO) technology. Additionally, the enVista lens is designed to minimize posterior capsular opacification, which is a common post-surgical complication with IOLs.

"I feel like this is a significant addition to my IOL armamentarium," Dr. Stephenson adds.

Full release of the enVista IOL is under way now that the coated insertion system has been approved. Additionally, the enVista toric lens has been approved in Europe and is in the pipeline in this country. REVIEW


Peter Heiner, MD

The enVista lens two weeks postoperatively.

Dr. Stephenson and Dr. Heiner are members of Bausch + Lomb's speakers bureau.

1. Werner L. Glistenings and surface light scattering in intraocular lenses. J Cataract Refract Surg. 2010;36(8):1398-1420.
2. Christiansen G, Durcan FJ, Olson RJ, Christiansen K. Glistenings in the AcrySof intraocular lens: a pilot study. J Cataract Refract Surg. 2001;27(5):728-733.


Posterior Segment Findings in SLE

A review of how to recognize and treat systemic lupus erythematosus-associated posterior segment disease.

By Robert W. Wong, MD, Austin, Texas, and Emmett T. Cunningham Jr., MD, PhD, MPH, San Francisco

The first use of the term "lupus," which is Latin for wolf, is attributed to the 12th-century physician Rogerius to describe the classic malar rash that resembles the pattern or fur on a wolf's face. Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by the production and deposition of autoantibody immune complexes in tissues throughout the body.[1] In the United States, the annual incidence is 5.1 per 100,000 persons with a reported prevalence of 52 cases per 100,000 population.[2] There exists a racial predilection, as the prevalence of SLE ranges from 40 cases per 100,000 persons among northern Europeans to more than 200 per 100,000 persons among blacks.[3] Lupus tends to be more common among women by a factor of 9:1.[4]

Systemic lupus erythematosus can affect virtually any organ in the body, and the American College of Rheumatology has set criteria for the diagnosis of SLE *(Table 1)*. Although ocular manifestations are not part of the diagnostic criteria, they are common and can be observed in up to one-third of patients with SLE.[5] Anterior segment findings in SLE include keratoconjunctivitis sicca, conjunctivitis, episcleritis, anterior scleritis, keratitis and iritis.[5] It is important to recognize SLE-associated posterior segment disease and its association with CNS disease as a significant cause of patient morbidity.

Posterior Segment Manifestations

• ***Retinopathy.*** The retinopathy associated with SLE is the most common type of posterior segment finding and the risk of retinal involvement varies with disease control. It may range from 3 percent in well-controlled patients to 29 percent in patients with more active systemic disease.[6,7] The most common retinal manifestation is cotton wool spots *(See Figure 1)*, although frank phlebitis and arteritis also occur, often producing venous or arteriolar occlusion, respectively *(See Figure 2, p. xx)*. Other manifestations may include microaneurysms, vascular tortuosity, arteriolar narrowing, retinal edema or exudates. Retinal microangiopathy associated with SLE is thought to represent immune complex-mediated vascular injury and microvascular thrombosis.[8] Fortunately, most patients with mild retinopathy are at low risk for vision loss.[6]

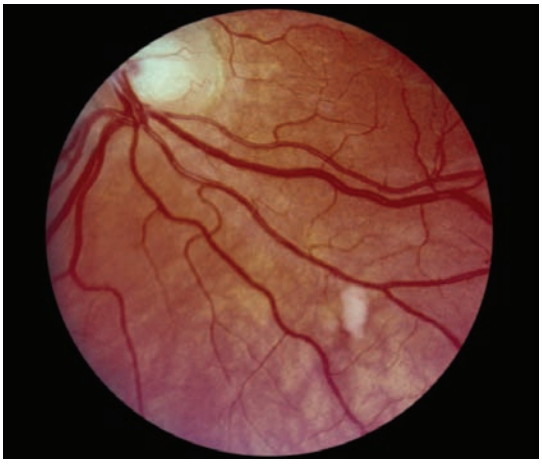


Figure 1. An isolated cotton-wool spot in a patient with systemic lupus erythematosus.

In contrast, SLE associated vaso-occlusive disease characterized by widespread capillary non-perfusion of the retina *(See Figure 3)* has been associated with a worse visual prognosis. Up to 55 percent of patients

This article has no commercial sponsorship.

(Modified from Tan, et al.[24])

Table 1. American College of Rheumatology Criteria for the Diagnosis of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging (Atrophic scarring may occur in older lesions)
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving ≥two peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis	A) Pleuritis: Convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or B) Pericarditis: Documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	A) Persistent proteinuria >0.5 g/d or >3+ if quantitation not performed, or B) Cellular casts: May be red blood cell, hemoglobin, granular, tubular or mixed
8. Neurological disorder	A) Seizures: In the absence of offending drugs or known metabolic derangements, or B) Psychosis: In the absence of offending drugs or known metabolic derangements
9. Hematological disorder	A) Hemolytic anemia: With reticulocytosis, or B) Leukopenia: <4,000/mm^3 total on ≥two occasions, or C) Lymphopenia: <1,500/mm^3 on ≥two occasions, or D) Thrombocytopenia: <100,000/mm^3 in the absence of offending drugs
10. Immunological disorder	A) Anti-DNA: Antibody to native DNA in abnormal titer, or B) Anti-Sm: Presence of antibody to Sm nuclear antigen, or C) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false-positive serological test for syphilis known to be positive for at least six months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption tests
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

Abbreviations: g = grams; d = deciliters; mm = millimeters; DNA = deoxyribonucleic acid; Sm = Smith; IgG = immunoglobulin G; IgM = immunoglobulin M.

Systemic lupus erythematosus can be diagnosed if any four or more of the 11 criteria are present serially or simultaneously, during any interval of observation.

may have vision worse than 20/200, and 40 percent of patients may go on to develop retinal neovascularization and vitreous hemorrhage.[9] Patients often require panretinal photocoagulation to treat areas of capillary non-perfusion. Some patients can develop anterior segment rubeosis, tractional retinal detachment[9] or macular infarction[10] leading to significant vision loss and morbidity. Increasing evidence suggests that this more severe vaso-occlusive form of lupus-related retinopathy may be associated with the presence of antiphospholipid antibodies, including the presence of anti-cardiolipin (aCL) or lupus anti-coagulant antibodies (LAC).[11]

There exists a relationship between SLE and the antiphospholipid antibody syndrome (APS). The "classical" clinical manifestations of APS, also known as Hughes' syndrome,[12] include deep venous thrombosis, cerebral arterial thrombosis, pulmonary emboli, recurrent fetal loss (predominantly in the second and third trimesters) and thrombocytopenia. Patients with at least one classical clinical manifestation of APS, along with the presence of antiphospholipid antibodies such as aCL and/or LAC antibodies in at least two samples taken three months apart, may be diagnosed with APS. Patients with APS may have SLE. However, if patients with APS do not meet the American College of Rheumatology criteria for SLE diagnosis, they can be diagnosed as having lupus-like disease (LLD) or primary APS.

The pathogenesis of antiphospholipid antibody-induced vascular thrombosis is not entirely understood, but the presence of aPL may increase plasma levels of endothelin 1 (ET-1), which could affect arterial tone and contribute to the occurrence of thrombosis.[13] Severe vaso-occlusive retinopathy, including central or branch retinal artery and vein occlusion with extensive retinal capillary nonperfusion, in patients with SLE with positive aPL or primary APS has been coined Hughes' retinopathy.[14] Patients with APS generally require anticoagulation to maintain a therapeutic international normal ratio (INR) of ≥3 to have

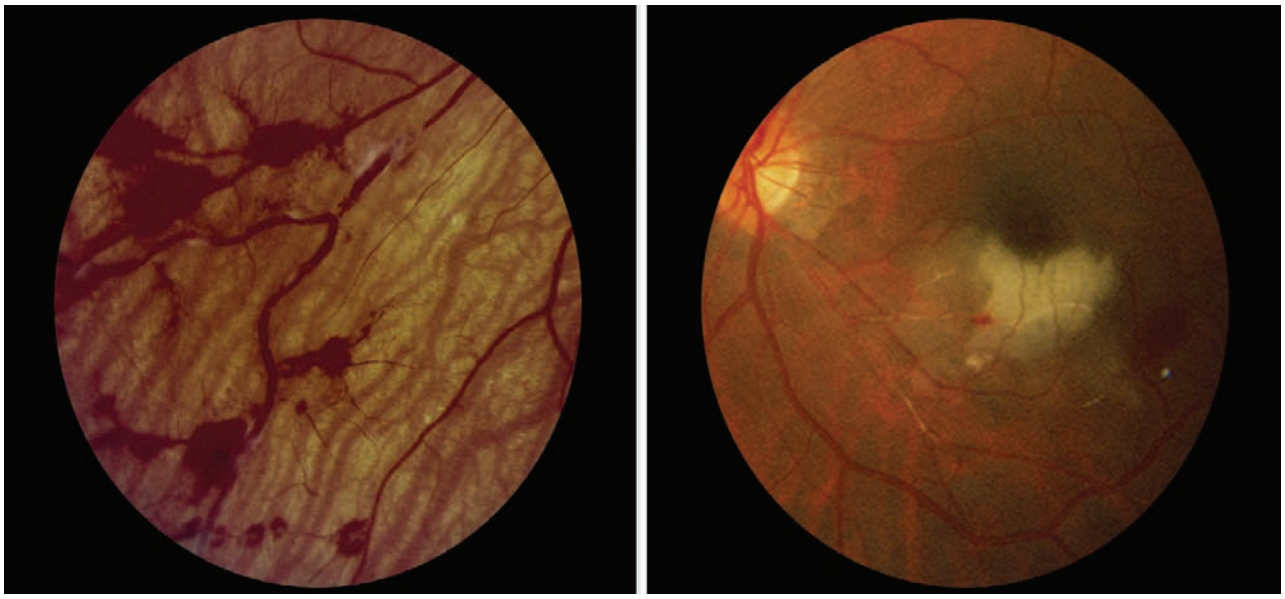


Figure 2. Peripheral phlebitis with venous occlusion (left) and posterior arteritis with arteriolar occlusion (right) in two separate patients with systemic lupus erythematosus.

adequate prophylaxis in preventing recurrent thrombosis. Cerebrovascular disease seems to be the most associated finding seen in SLE patients with Hughes' retinopathy,[14] and proper neurological workup should be taken into consideration. Some recommend that patients with SLE and antiphospholipid-associated Hughes' retinopathy should be started on anticoagulation in addition to treatment of the underlying rheumatological disease.[14]

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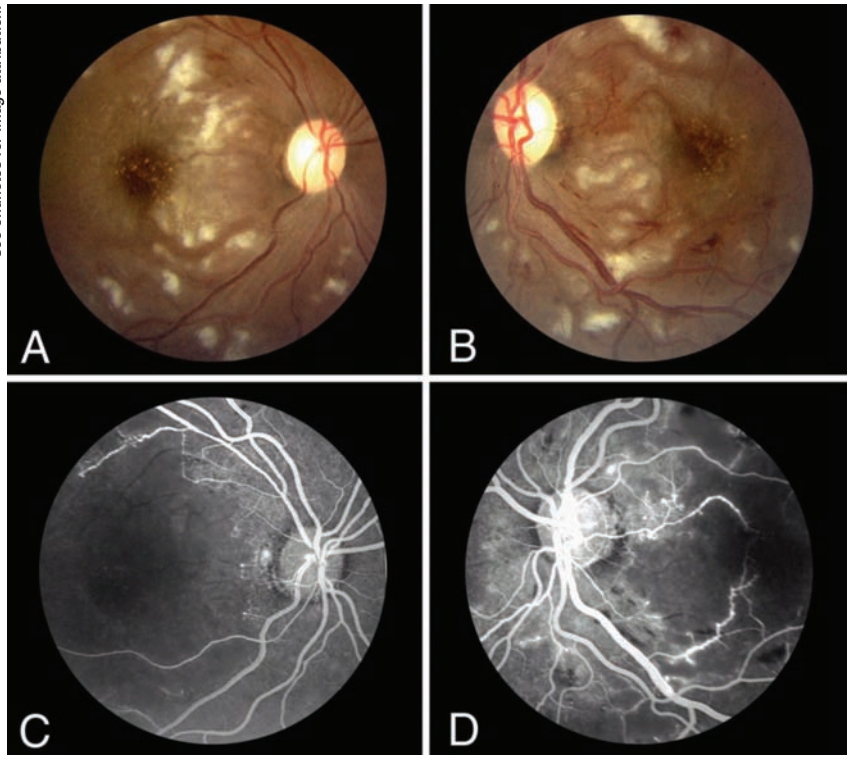

Figure 3. Color photographs (A,B) and early-phase fluorescein angiograms (C,D) showing extensive arteriolar occlusions with bilateral macular infarctions in a patient with systemic lupus erythematosus. Vision loss was the presenting sign of lupus in this patient.

• ***Posterior scleritis.*** Posterior scleritis can occur in patients with SLE and may sometimes be the presenting sign of systemic disease.[15] Symptoms may include vision loss, red eye and/or pain in one or both eyes. Ocular signs suggestive of posterior scleritis include exudative retinal detachment, thickened posterior sclera and fluid seen in sub-Tenon's space on ocular ultrasonography *(See Figure 4)*. Though rare, one case of SLE presenting as giant nodular scleritis has been reported, and this finding may mimic a choroidal melanoma.[15] With prompt treatment with systemic or periocular corticosteroids, visual prognosis can be good.

• ***Choroidopathy.*** Choroidopathy in SLE may present as multiple, serous detachments of the retinal pigmented epithelium and the neurosensory retina *(See Figure 5)*.[16-18] Visual loss can occur if the detachment affects the macula. In some cases, the subretinal fluid can

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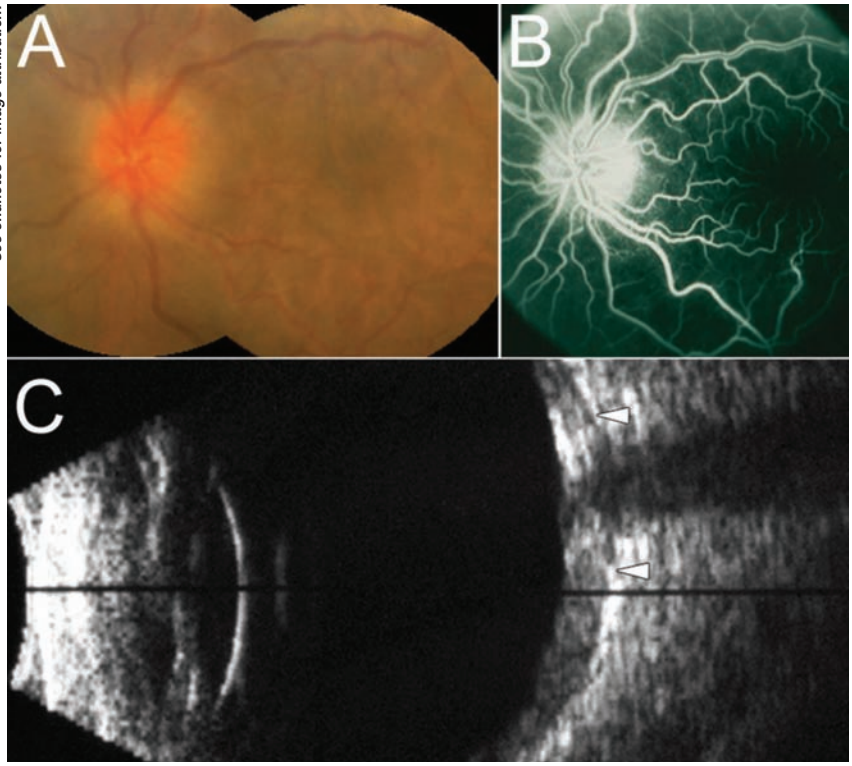

Figure 4. Posterior scleritis in a patient with systemic lupus erythematosus. Optic disc hyperemia and retinal striae were evident clinically (A, B). B-scan ultrasonography showed posterior eye wall thickening with retrobulbar fluid producing the so-called "T-sign" (C).

progress to large, bullous exudative retinal detachments. Treatment of underlying active disease often results in resolution of the choroidopathy and associated subretinal fluid. Once the fluid resolves, the fundus may be left with a mottled appearance to the pigmented epithelium. Patients with SLE-associated choroidopathy tend to have associated systemic vascular disease either from systemic hypertension or lupus nephritis, vasculitis or a combination of these.[17] Suspected pathogenesis may be due to a microangiopathy caused by a mononuclear inflammatory infiltrate of the choroid, immunoglobulin and complement deposition in the choroidal blood vessels and damage to the overlying RPE.[17] It is postulated that systemic hypertension may contribute to the serous detachments by providing a hydrostatic force across and into the detachment.[17] Of course, many patients with SLE are treated with systemic corticosteroids, and the relationship between corticosteroids and serous retinal detachment can be complex. That said, choroidopathy has been reported in SLE without prior exposure to corticosteroids,[19] and the majority of cases of SLE-choroidopathy resolve with treatment with systemic immunosuppression including corticosteroids.[17]

• ***Optic neuropathy***. While the involvement of the CNS occurs in nearly 39 percent of patients with SLE,[20,21] the estimated prevalence of optic neuropathy in SLE is 0.7 percent.[20] Though rare, the clinical features of optic neuropathy in patients with SLE have been described, and its presentation can be highly variable. For example, a patient may present with painless vision loss, arcuate visual field defects and optic disc swelling when seen with anterior ischemic optic neuropathy, or rather with significant orbital pain associated with optic neuritis or papillitis.[22] Reported ocular findings may include optic neuritis, ischemic optic neuropathy, retrobulbar optic neuropathy and optic atrophy, and optic nerve disease can affect one or both eyes.[22,23] Corresponding visual field deficits, depressed visual evoked responses and afferent pupillary defects have been observed. Visual prognosis may also be variable as well, ranging from 20/20 to NLP vision depending on the extent of optic nerve damage, and this may be corticosteroid-responsive.[22] The pathogenesis is thought to be related to small-vessel occlusive disease of the optic nerve, where milder cases show demyelination from mild ischemia and more severe cases exhibit significant axonal damage and necrosis.[22] Of import is the association of optic nerve disease and associated CNS lesions in patients with SLE. Central nervous system lesions have been estimated to be in 54 percent of patients with lupus optic neuropathy, most commonly affecting the spinal cord.[22]

Treatment Options

Managing posterior segment disease typically involves the use of systemic immunosuppression with corticosteroids in the acute setting, followed by non-corticosteroid immunosuppresive agents. For severe posterior segment involvement, intravenous corticosteroid pulse therapy may be needed acutely. In some cases, local treatment with periocular corticosteroid injection may be useful. Patients with severe vaso-occlusive disease, particularly with the presence of antiphospholipid antibodies, may benefit from additional anticoagulation and/or anti-platelet treatment. In patients with profound retinal ischemia, panretinal photocoagulation and vitrectomy surgery may be needed to address complications

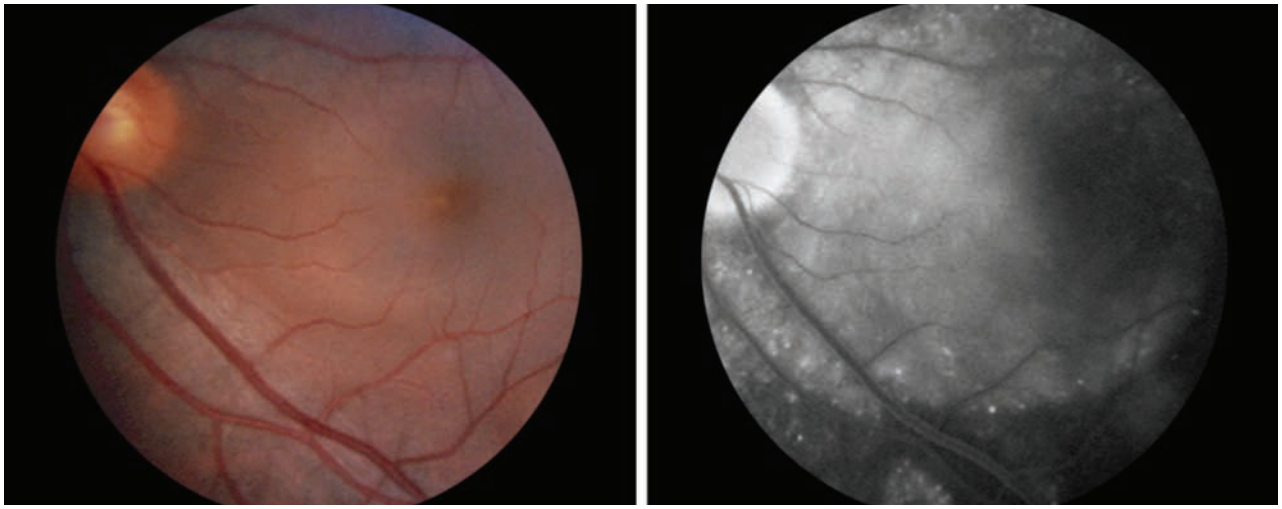

Figure 5. Serous retinal detachments in a patient with systemic lupus erythematosus choroidopathy. Similar findings were present in the fellow eye.

from anterior or posterior segment neovascularization.

The Role of the Retina Specialist

Retinal specialists serve an important role in the overall care of patients with SLE. One large prospective study showed that 88 percent of SLE patients with retinopathy had active systemic disease.[7] The SLE patients who developed retinopathy had a lower overall survival rate as compared to patients without retinopathy over the same time period. Moreover, active CNS involvement of lupus, a significant cause of patient morbidity, is found more often in patients with active retinopathy,[7,14] retinal vaso-occlusive disease[9] and optic neuropathy.[22] Therefore, the presence of posterior segment findings in patients with SLE should prompt the retinal specialist to communicate with the general internist and/or rheumatologist regarding the activity and severity of their mutual patients' disease. REVIEW

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Figure 3 reproduced with permission from Shein J, Shukla D, Reddy S, Yannuzzi LA, Cunningham ET Jr. Macular infarction as a presenting sign of systemic lupus erythematosus. Retina Cases & Brief Reports 2008;2:55-60.

Figure 4 reproduced with permission from Wong RW, Chan A, Johnson RN, McDonald HR, Kumar A, Gariano R, Cunningham ET Jr. Posterior scleritis in patients with systemic lupus erythematosus. Retinal Cases & Brief Reports 2010;4:326-331.

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Lower Eyelid Malposition: Evaluation and Treatment

A review of the causes and surgical approaches to lower eyelid malpositions that clinicians encounter most often.

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Malposition of the lower eyelid can result from a host of causes, with consequences ranging from discomfort to the potential to threaten eye health. This article will review the types and possible causes of the most common lower-lid malpositions encountered in clinical practice. While a detailed discussion of the various surgical approaches is beyond the scope of this article, we will review the recommended approaches to surgical repair.

The Mechanisms

It is useful to conceptualize the eyelid as comprising three lamellae: 1) anterior—skin and orbicularis muscle; 2) middle—orbital septum and eyelid retractors; and 3) posterior—tarsus and conjunctiva. This model provides a framework for understanding the mechanisms of eyelid malposition and approaches to surgical correction. In general, there are three types of lower eyelid malpositions: entropion; ectropion; and retraction. These are discussed below and summarized in Table 1.

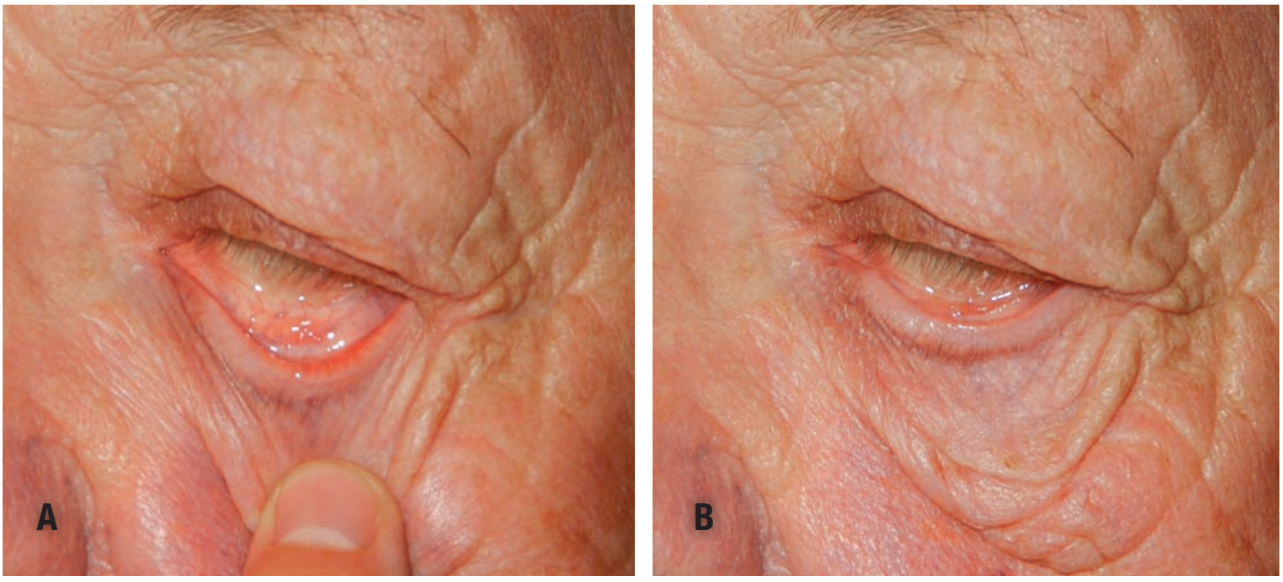

Figure 1. Abnormal eyelid snap test in an elderly patient. A. The lower eyelid is pulled away from the globe. B. On release of the lower eyelid, it fails to promptly "snap back" into position against the globe, indicative of poor orbicularis oculi muscle tone.

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Table 1. Overview of Lower Eyelid Malpositions, Etiologies and Surgical Approaches

Type of Malposition	Etiology	Surgical Approach
Ectropion	Congenital	Add additional skin (via flap or graft) and possible horizontal tightening of eyelid
	Mechanical	Remove mass lesion, if present, and horizontally tighten eyelid
	Involutional	Horizontally tighten eyelid
	Cicatricial	Add additional skin (flap or graft), release any vertical scar bands, horizontally tighten eyelid
	Paralytic	Horizontally tighten eyelid, possibly reinforced by periosteal flap or fascial sling; palpebral spring
Entropion	Congenital	Depends upon specific pathophysiologic mechanism, e.g. advancement of lower eyelid retractors
	Involutional	Horizontally tighten eyelid and advance lower eyelid retractors
	Spastic	Everting sutures, botulinum toxin injections
	Cicatricial	Many corrective procedures described, including blepharotomy or tarsotomy with eyelid margin rotation, recession of the anterior lamella, mucous membrane graft
Retraction	Nonthyroid proptosis	May reduce the degree of proptosis via orbital decompression or advancing the orbital rim (direct advancement vs. orbital rim onlay implant) or raise the lower lid via a rigid spacer graft in the middle lamella (may need to lengthen anterior and/or posterior lamella if there is a tissue shortage)
	Cicatricial	Recess lower eyelid retractors, release any tractional scar bands, rigid spacer graft in middle lamella and lengthening of anterior and/or posterior lamella if there is a tissue shortage
	Thyroid	Same as for nonthyroid proptosis and cicatricial retraction since both proptosis and middle lamellar scarring contribute to the eyelid retraction; wait for thyroid eye disease to become inactive (clinical activity score = 0) before eyelid repositioning

Numerous factors interplay to influence eyelid position and orientation. For example, horizontal laxity may destabilize the lower eyelid, causing the eyelid to turn outward or inward, depending on anatomic comorbidities, such as deficiency of the anterior or posterior lamella, prominence of the globe and orbicularis oculi muscle tone. Examination should document the lower eyelid margin and punctal position, degree of eyelid laxity (by the eyelid distraction test), orbicularis tone (by the "snap test"), orbicularis muscle strength (on forced eyelid closure), and size of the tear lake, in addition to any trichiasis and exposure keratoconjunctivitis.

On the snap test, when the lower eyelid is everted in the presence of normal muscle tone, the eyelid should return to its proper position against the globe within a second or two, even without an eyelid blink. If there is poor muscle tone, which may be found with facial nerve palsy, myopathy or advanced age *(See Figure 1)*, the lower eyelid slowly swings back against the globe, taking several seconds or awaiting a blink to pull the eyelid inward. A lax lower eyelid with poor orbicularis muscle tone tends to swing outward, away from the globe, succumbing to the effect of gravity, resulting in ectropion.

Entropion

Entropion is characterized by inward rotation of the eyelid margin *(See Figure 2)*, which may result in pain and corneal injury. The etiology may be involutional, cicatricial, spastic or, rarely, congenital. Involutional entropion typically involves horizontal eyelid laxity with dehiscence of the eyelid retractors and override of the preseptal over the pretarsal orbicularis oculi muscle. Spastic entropion is due to excessive contraction of the orbicularis muscle. Cicatricial entropion *(See Figure 3)* involves a tight posterior lamella due to scarring of the conjunctiva and/or tarsus. This scarring may result from trauma, surgery, or cicatrizing conjunctivitis due to infection (e.g., trachoma), topical medications (pseudopemphigoid), or a systemic disorder such as ocular cicatricial pemphigoid (OCP) or Stevens-Johnson syndrome. The etiology of the entropion must be understood before proceeding with treatment, as it will impact the choice and timing of surgery. For example, OCP must be

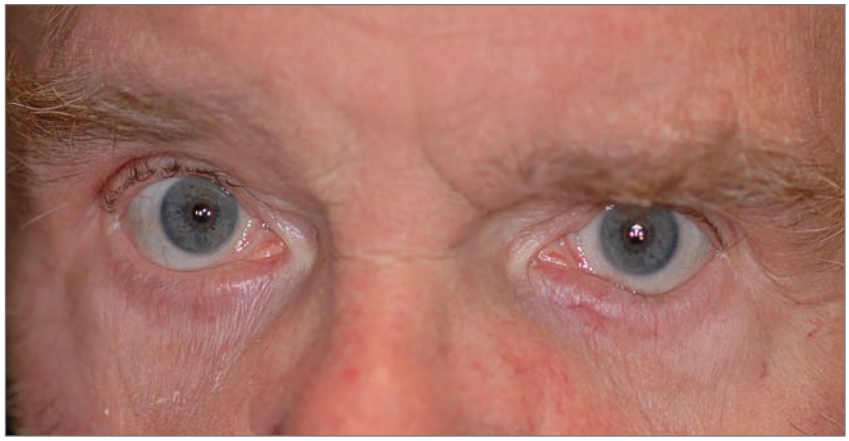

Figure 2. Involutional entropion of the left lower eyelid. Note that the eyelashes are rotated inward. There is the characteristic "roll" of tissue just below the left lower eyelid margin due to the preseptal orbicularis oculi muscle overriding the pretarsal muscle.

treated with systemic immunomodulatory therapy before surgery. Cicatricial entropion usually displays visible conjunctival scarring and/or symblepharon, altered eyelid margin architecture and characteristic response to digital eyelid eversion. With involutional entropion, if you evert the eyelid to its proper anatomic position, it will usually stay in this position for at least a few seconds after releasing the eyelid, often until the patient blinks. With cicatricial entropion, when the eyelid is released, it promptly turns inward again.

Regarding treatment of entropion, everting (Quickert) sutures may be used. This consists of placing three horizontal mattress sutures (medially, centrally and laterally, with all sutures lateral to the punctum) from the inferior conjunctival fornix out through skin just below the lash line. The lower the sutures are placed in the fornix, and the closer they are to the lash line as they exit the skin, the greater the everting effect. Everting sutures are quite effective as a temporary measure, but are generally not believed to provide long-term correction. Taping of the lower eyelids is often used for elderly patients, although this is difficult to do effectively and may cause skin irritation. Botulinum toxin injections may have a role in spastic entropion.

Numerous surgical procedures have been reported for repair of entropion. For involutional entropion, successful corrective surgery usually combines horizontal tightening of the eyelid (usually via the lateral tarsal strip procedure), advancing the lower eyelid retractors, and, when needed, the creation of a full-thickness eyelid scar to prevent the preseptal orbicularis muscle from overriding the pretarsal muscle. Recent reports suggest that the combination of horizontal eyelid tightening and Quickert sutures can be quite successful in involutional entropion.

Cicatricial entropion repair is somewhat more complex, and the choice of the specific corrective procedure depends upon the severity of the entropion and surgeon preference. Surgical repair usually involves an eyelid margin rotation procedure or anterior lamellar recession, with or without a mucous membrane graft. Severe cicatricial entropion can be difficult to successfully repair, and it's extremely important that appropriate treatment be directed toward the underlying cause, when indicated, e.g., OCP, Stevens-Johnson syndrome or trachoma. Otherwise, there is a high likelihood that the entropion will recur postoperatively.

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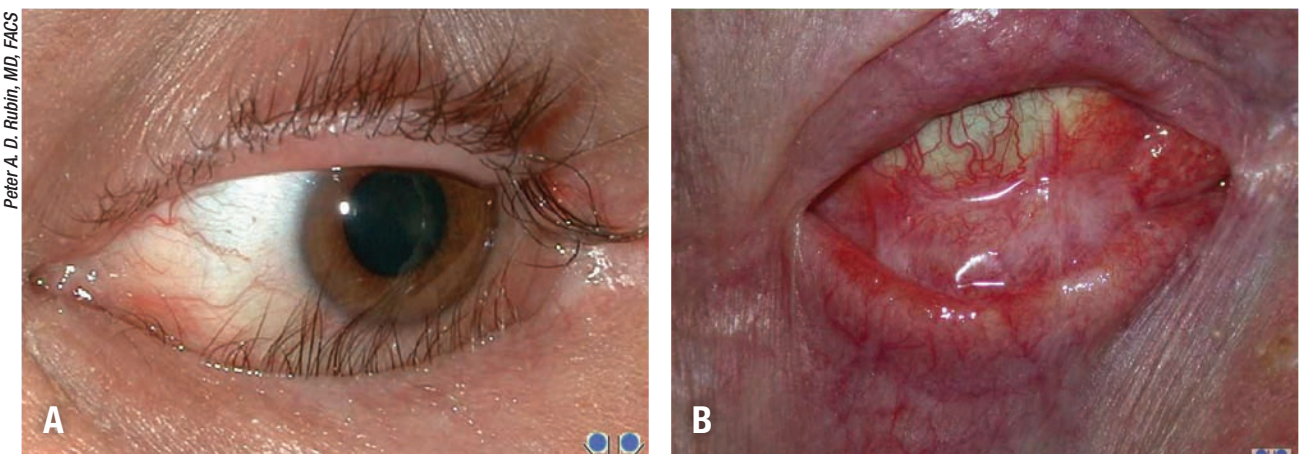

Figure 3. A. Cicatricial entropion of the lower eyelid following transconjunctival orbital floor fracture repair. B. Ocular cicatricial pemphigoid. Note the conjunctival injection, indicative of active disease, and the extensive inferior symblepharon due to the severe, progressive cicatrizing conjunctivitis.

Ectropion

Ectropion denotes outward rotation of the eyelid margin *(See Figure 4)*. The etiology may be classified as involutional, cicatricial, paralytic, mechanical or congenital. Mechanical ectropion can be seen when the lower eyelid is very swollen or there is a large mass lesion, particularly in the face of severe horizontal eyelid laxity. Cicatricial ectropion may result from skin shortage and/or scarring, e.g., due to surgery, trauma, sun damage or chronic dermatitis. Congenital ectropion often shares with cicatricial ectropion the common factor of skin shortage. Facial nerve palsy often results in paralytic ectropion *(See Figure 5)*, particularly in the elderly. Ectropion may produce exposure keratoconjunctivitis and/or tearing. Both entropion and ectropion may cause inferior corneal ulceration, which is an urgent indication for surgical repair.

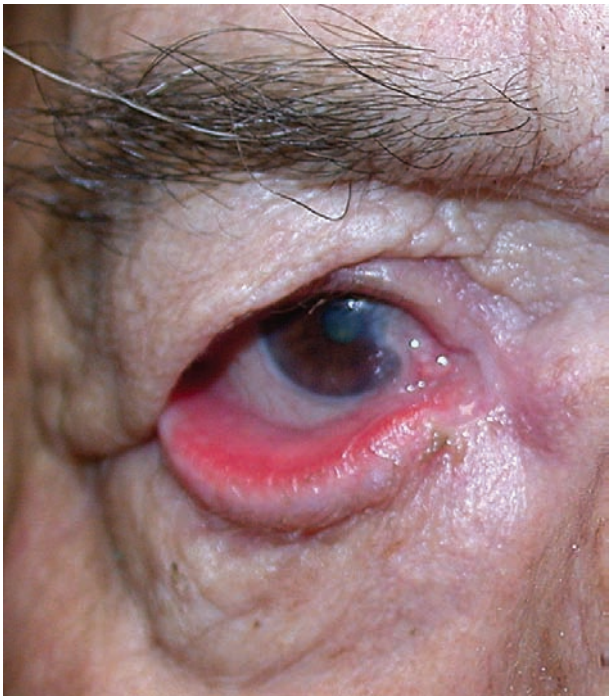

Figure 4. Severe involutional ectropion of the right lower eyelid. There is conjunctival injection and eyelid margin keratinization due to chronic exposure. The patient also has severe upper eyelid dermatochalasis and a pterygium.

The mainstay of ectropion repair remains horizontal tightening of the eyelid, usually via lateral canthal tendon tightening, as full-thickness eyelid wedge resection carries the risk of an eyelid margin notch and trichiasis. Medial or punctal ectropion may be addressed by excision of a horizontal ellipse of conjunctiva below the lower punctum. If there is severe medial canthal tendon laxity, then successful repair may require tightening of the medial canthal tendon, which is somewhat more technically challenging than lateral canthal tendon tightening. Paralytic ectropion, due to denervation of the orbicularis oculi muscle or severe myopathy, is corrected by horizontal tightening of the eyelid that may need to be supported by a fascial sling or permanent medial or lateral tarsorrhaphy. In the setting of cicatricial ectropion, skin shortage must be addressed by adding more lower eyelid skin via a full-thickness skin graft, a myocutaneous flap or an internal cheek (suborbital orbicularis oculi fat, or SOOF) lift.

Lower Lid Retraction

Lower lid retraction *(See Figure 6)* is commonly defined as a lid margin position below the inferior limbus (inferior scleral show). There is a broad differential diagnosis for eyelid retraction, and this has been well-reviewed by George Bartley, MD.[1] Thyroid eye disease is, by far, the most common cause of eyelid retraction, although non-thyroid proptosis, severe lid laxity or eyelid scarring may also be responsible. The appropriate treatment depends on the underlying cause. In the case of thyroid eye disease,

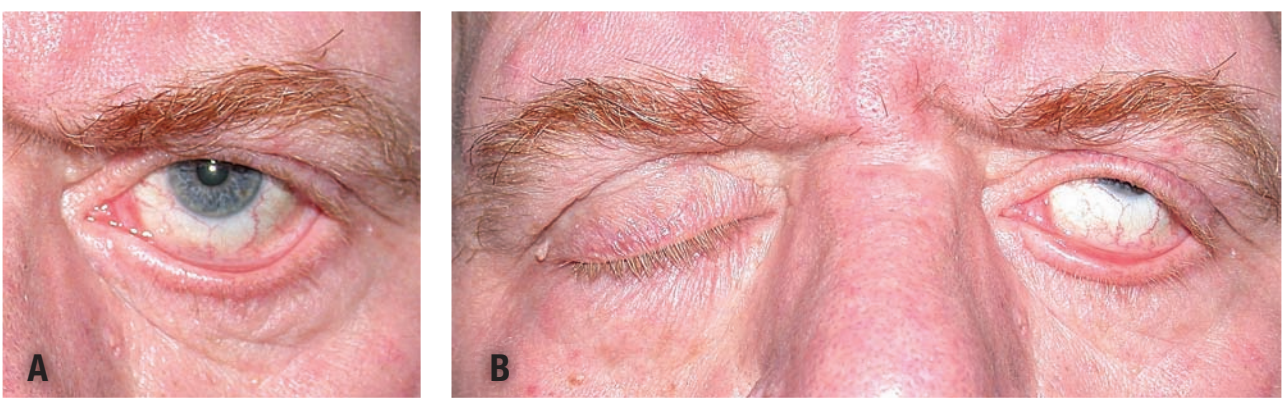

Figure 5. A. Paralytic ectropion of the left lower eyelid due to left facial nerve palsy. B. Severe left lagophthalmos is evident on eyelid closure due to orbicularis oculi muscle weakness.

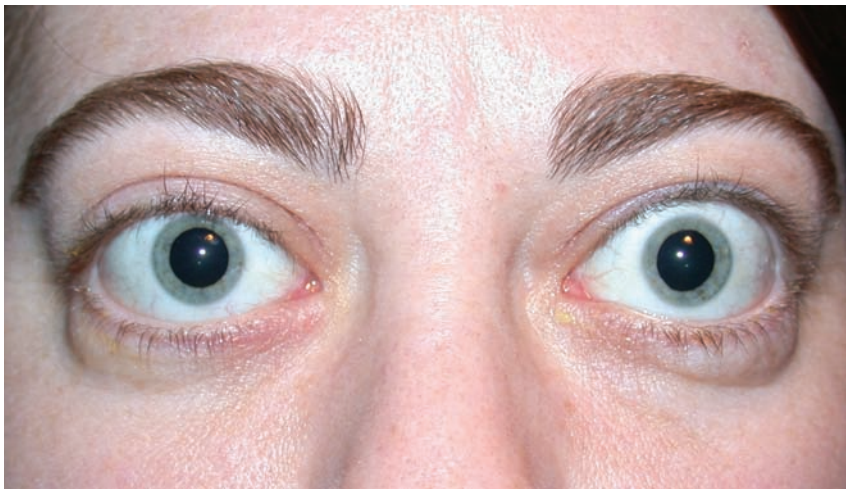

Figure 6. Bilateral upper and lower eyelid retraction due to thyroid eye disease, the most common etiology of eyelid retraction.

non-urgent surgery should usually be delayed until the eye condition is stable and inactive. Involutional retraction (sagging) of the lower eyelid may result from horizontal eyelid laxity, while cicatricial retraction results from scarring in the middle lamella (lower eyelid retractors and orbital septum).

Regarding treatment, hyaluronic acid dermal filler injection has been shown to modestly improve lower eyelid retraction, as a nonsurgical alternative in patients with exposure keratopathy due to eyelid retraction. The nature of the surgical repair undertaken depends upon the cause of the retraction. In the case of a lax, sagging lower eyelid, horizontal tightening should be sufficient. If the lower eyelid retractors are tight, then they should be recessed. If the globe is proptotic, then either supra-placing the lateral canthal angle or placing a rigid spacer graft, e.g. hard palate, in the middle lamella of the lower eyelid will be required. Any scar tissue contributing to the eyelid retraction, such as fibrosis to the inferior orbital rim or an alloplastic plate following orbital floor fracture repair, should be surgically divided. A temporary Frost suture, placing the lower eyelid on upward stretch, is commonly employed following surgery.

Lower eyelid malposition is commonly encountered in clinical practice. Symptoms can range from none to tearing or severe pain. Patients can develop vision-threatening sequellae, such as a corneal ulcer, and they may have an underlying systemic disorder. Prompt evaluation and management will protect the eye and allow early detection of an underlying systemic medical condition. REVIEW

Dr. Weinberg is in private practice in Concord, N.H.

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(continued from page 28)

chamber. That will let you loosen the adhesions that have formed by three weeks. Then you just rotate the lens to the proper position and remove the viscoelastic. In my experience, the lenses stay in place after this."

• ***If you have to reorient a lens, get help at astigmatismfix.com.*** "This site offers a formula created by John Berdahl and David Hardten," says Dr. Davison. "If a toric lens has moved, you enter the current refraction and where the lens is oriented, and the formula will tell you the correct axis the lens should be left at after reorientation."

Target: The Best Possible Vision

"I think toric lenses are vastly underutilized," says Dr. Osher. "No ophthalmologist in the office would identify a significant amount of astigmatism and ignore it. Everyone would at least give the patient a pair of glasses that corrects both the spherical refractive error and the astigmatism. We have the same technology in surgery, so we should always offer the patient correction of his astigmatism in addition to the correction of the spherical error. I believe that this will become the new standard of care, and toric lenses are a key part of that.

"I'm absolutely sure that the future will bring us more sophisticated—and unfortunately, more expensive—technologies that nail the target meridian," he continues. "The only way the full potential of advanced technology lenses such as torics or multifocals will be reached is to have either the diagnostic, preoperative technology or the intraoperative technology to confirm emmetropia on the spherical side, and make sure the axis is dead-on on the cylindrical side of the equation. This should be our noble goal, and I believe it's within our reach." REVIEW

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#1 PRESCRIPTION ALLERGY EYE DROP[1]

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Prescribe the Number One prescription allergy eye drop to Start and Finish the day with Zero-itch.[1,2]

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*Post-hoc 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. †(N=85; 95% CI=48.8, 70.5) ‡(N=82; 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.

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

DOSAGE 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 5% 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, sinusitis 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 and 200 mg/kg/day, respectively. Based on a 40 µL drop size and a 50 kg person, these doses were approximately 150,000 and 50,000 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an in vitro bacterial reverse mutation (Ames) test, an 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 100,000 times 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

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Glaucoma Therapeutics 2013

A look at the safety and efficacy of various therapies for the disease, from pharmaceuticals to surgical implants.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Robert David, MD, Aron Shapiro and James McLaughlin, PhD
Andover, Mass.

Primary open-angle glaucoma is a condition with a large number of treatment strategies, from drugs to devices to surgical interventions. The most effective drugs are available as generics or will be coming off patent soon. The stability of the therapeutic choices available (there hasn't been a new class of glaucoma drug in more than 15 years) might lead you to think that it's a disease that is under control with existing treatments, yet it remains a disease without a cure, a disorder with a significant ocular morbidity, and is the second-leading global cause of blindness. Of the 60 million people with this disease worldwide,[1] 15 percent will have a severe degree of permanent visual impairment.

With the host of new therapies that are on the horizon, it's a good time to peruse the pipeline, take a snapshot of the newest treatment modalities in various stages of development, and also examine issues that will confront efforts at therapeutic progress in the coming years.

IOP-lowering Drugs

Despite its close association with elevated intraocular pressure, glaucoma is a disease manifested at the level of the retinal ganglion cell layer,[2] and in any new development strategies, the importance of preserving visual function should be stressed as the ultimate clinical endpoint. This hasn't been the case so far; in a recent review of the newest surgical procedures, out of 100 clinical trials surveyed, only one used visual function as an endpoint.[3]

Since their introduction to the market in the mid-1990s, prostaglandin analogues have moved to the top of the list for patients with mild to moderately elevated IOP.[4] They are highly effective at reducing IOP via an enhancement of aqueous humor outflow through the uveo-scleral space. A number of other drugs, including β-adrenergic antagonists and carbonic anhydrase inhibitors, are also available. These agents reduce the production of aqueous humor to lower intraocular pressure and, while effective, require b.i.d. or t.i.d. dosing that makes compliance an issue and can significantly compromise therapeutic outcomes.[4] The fourth current class of medications, the α2 adrenergic agonists, also act by decreasing the production of fluid by the ciliary body and enhancing outflow. Combination agents that take advantage of complementary mechanisms of action are also available.[4] In addition, there are several new agents with novel pharmacodynamics in mid- and late-stage development that will add to the current arsenal of IOP-lowering compounds.[5]

One approach to enhance aqueous humor outflow through the physiological pathway is to use agents designed to relax the tension in the trabecular meshwork. The TM is a tissue that is physiologically similar to muscle in that the tensile status of the myosin-actin complexes within the cells are highly dynamic, and are regulated in large part by the action of Rho GTPase kinase (ROCK).[6] ROCK phosphorylation acts in at least three ways to increase contractile tension in the TM: directly, via phosphorylation of myosin light chain; and indirectly through inhibition of MLC phosphatase and activation of Lim kinases. A couple of ROCK inhibitors (AMA0076, Amakem Therapeutics; AR12286, Aerie Pharmaceuticals)

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are in clinical development, including testing of combination therapies (AR12286 plus latanoprost). The list of new IOP lowering agents also includes LM7101, a Lim kinase 2 inhibitor (Lexicon Pharmaceuticals).

A different class of agents in development targets adenosine receptors; for example, the adenosine R1 agonist INO-8875 (Inotek) has shown promise in Phase I and Phase II for IOP reduction in patients with ocular hypertension. This compound works by enhancing outflow through the physiological pathway by stimulating the secretion of matrix metalloproteinases, enzymes that mediate connective tissue remodeling of the TM. Several other adenosine receptor-targeted therapies include ACN-1052 (Acorn Biomedical) and CF-101(Can-Fite BioPharma), but unlike the Inotek compound these drugs are aimed at the adenosine A3 receptor. Targeting this signaling pathway reduces IOP by inhibiting aqueous humor production of the ciliary epithelium. These compounds are also formulated for oral rather than topical dosing, a choice that may provide a greater duration of action and less IOP fluctuation.

Two other additions to the development pipeline are in early-phase clinical trials. One of these is a dose-ranging study of the mixed prostaglandin agonist ONO-9054 (Ono Pharma). Another dose-escalation trial is under way for SYL040012 (Sylentis). The Sylentis compound is an RNAi-based compound designed to target the same β-adrenergic pathway targeted by timolol. Instead of acting as a traditional receptor antagonist however, SYL040012 blocks the pathway by inhibiting biosynthesis of the receptor protein.

New Delivery Systems

One of the greatest hurdles in controlling IOP by means of medical treatment in glaucoma patients is that of compliance: The combination of the chronic nature of treatments, the lack of symptoms and the age of the affected population is a recipe for poor compliance. Recent estimates suggest that 60 percent of patients fail to maintain a daily medication regimen.[7] One approach to this problem is to take the task out of the hands of the patient by employing sustained-release or other depot forms of existing drugs. A number of strategies employing this approach to drug delivery are currently in development.

Depot forms of effective drugs such as the travoprost punctal plugs (Ocular Therapeutix) are currently in clinical trials. In a recent Phase II study presented at the 2011 meeting of the American Glaucoma Society, German researcher Norbert Pfeiffer, MD, found that the travoprost-containing plugs provided a sustained IOP lowering effect of at least 6.6 mmHg that persisted for two months. Another delivery vehicle is a variant of the contact lens and is designed to reside under the lid rather than on the cornea. This device is in development at Amorphex Therapeutics, and can deliver drugs to the eye in a continuous, slow-release fashion; it is particularly easy to place or exchange if needed. Polymerized collagen gels (Euclid Systems) are a biodegradable matrix suitable for depot delivery, as demonstrated for slow release of latanoprost *in vitro*. *(Devore DP, et al. IOVS 2011;52:ARVO E-Abstract 3421)* Perhaps a bit further into the future we can expect to see nano-particle based depot delivery of drugs from companies such as Icon Bioscience.

IOP Monitoring Devices

Diurnal variations of IOP have been thought to play an important role in progression of disease for some time.[2] Office visit assessments provide a single measure of IOP, so they cannot provide a comprehensive picture of daily IOP fluctuations. The arrival of continuous monitoring devices designed to provide a round-the-clock IOP measurement is a welcome step forward.

A number of different technologies in development can provide continuous IOP monitoring. One approach uses implantable micro-sensors that transmit pressure data to a handheld external device (Implandata Ophthalmic Products). Another implantable device, the iSense (AcuMEMs), is also in development. Both the Implandata and AcuMEMs systems would be implanted during cataract surgery or another surgery to allow access to the anterior chamber. An alternative technology employs a contact lens with an embedded strain gauge (Triggerfish; Sensimed AG) to record continuous 24-hour changes in ocular surface tension. While this metric is distinct from a true measure of IOP, it provides an indirect means to monitor the fluctuations associated with IOP. Using this device, a recently published study showed a nocturnal peak in tension occurs in about 70 percent of all patients with diagnosed or suspected POAG.[8] These continuous measurement devices will likely have a significant impact on therapy of POAG going forward.

IOP-lowering Devices

Surgical approaches to reducing IOP remain an important treatment option in glaucoma therapy, but an expanding alternative to laser-based surgery that can effectively address the compliance issue is the use of implantable stents and other devices that improve the function of aqueous outflow. With few exceptions, these devices are implanted in patients during cataract surgery (similar to the IOP devices listed above) and

so are relatively low-risk. Several such implantable devices are either new to the market or in late-stage development, and each employs its own unique approach to the engineering challenge of increasing outflow. The Hydrus microstent (Ivantis) is designed to act much like a cardiac stent; it's placed in the canal of Schlemm and maintains a patent canal that can mediate aqueous drainage. In a recently reported trial, the patients receiving the device maintained an IOP of 21 mmHg or less without medication for six months. Another device in development is the Cypass (Transcend Biomedical), a thin polymer tube that creates a new outflow pathway when inserted under the scleral spur into the supraciliary space. A different kind of surgically implantable treatment is the stent from AqueSys. The device is a gelatin tube that is a thin rod in its dehydrated form, but when inserted becomes hydrated and soft in order to form a path for aqueous humor outflow.

The Glaukos iStent connects the anterior chamber with Schlemm's canal to facilitate outflow.

The newest addition to the list of approved implants is the Glaukos iStent, which was approved by the Food and Drug Administration in June 2012.[9] This device is a titanium tube which bypasses the TM and provides a direct connection between the anterior chamber and Schlemm's canal. In multiple clinical trials the device was shown to decrease IOP to a greater extent than cataract surgery alone and, in doing so, provide a long-term solution to compliance issues for patients with ocular hypertension. The iStent indication limits it to patients undergoing cataract surgery, however, which reduces the number of eligible patients but also minimizes the need for additional surgical procedures. Long-term follow-up of the iStent will include five-year monitoring of patients from completed studies for safety issues such as best-corrected acuity loss, endophthalmitis, retinal detachment, choroidal hemorrhage and aqueous misdirection. It's interesting to note that while the efficacy endpoint for the iStent is reduction in IOP, it's the safety assessment of the device that will tell the real story, since any glaucoma therapy should have, as an ultimate goal, the minimization of decremental loss of visual function.

Targeting Neuroprotection

While current therapies, surgeries and the growing list of devices focus on lowering IOP as the path to successful glaucoma therapy, there have also been some advances in more direct approaches to treatment and prevention of the glaucomatous neuropathology that leads to visual loss.[2] A key point in understanding the pathology underlying POAG is that while lowering IOP shows a strong correlation with minimizing disease progression, the connection is not absolute: Patients with normal pressures can show visual field loss, while the visual fields in others with high IOPs may remain intact. Increasingly, then, the focus of clinicians and researchers has turned to addressing the pathological consequences of the disease.

A growing body of evidence suggests that many of the drugs that are used to treat elevated IOP also have neuroprotective effects.[10] For example, there is ample evidence that inflammatory cytokines from neighboring microglia are important contributors to retinal degeneration, and recent studies suggest that α2 adrenergic agonists can minimize cytokine release, perhaps through activation of brain-derived neurotrophic factor or other neurotrophic pathways.[11-13] A clinical study in patients with normal-tension glaucoma has suggested that brimonidine (Alphagan) has an effect beyond lowering IOP.[14] Similarly, β-adrenergic antagonists, prostaglandin F2α agonists and carbonic anhydrase inhibitors all have established neuroprotective actions that may provide a therapeutic benefit beyond their IOP-lowering action.[8,15,16]

Interest in neuroprotection is evident from clinical studies of the glutamate receptor antagonist memantine, animal studies of other glutamate antagonists and experimental trials with other drugs with known neuroprotective effects.[17,18] Promising animal studies suggest other avenues of addressing the goal of neuroprotection. For instance, the tumor necrosis factor-α (TNF-α) inhibitor Etanercept has been shown to effectively prevent RGC loss in a rodent glaucoma model.[19] The established association between retinal degeneration seen in POAG, β-amyloid deposition and the more global neurodegeneration of Alzheimer's disease may provide a route for basic scientific advances as well as new clinical approaches.[20] One compound that has shown the ability to reduce β-amyloid

aggregation in animal models of glaucoma, MRZ-99030 (Merz Pharmaceuticals GmbH), is currently the subject of clinical trials to assess the safety of a topical formulation (NCT01714960) at clinicaltrials.gov.

Overall, the dual-action nature of many current glaucoma therapies seems to be a serendipitous consequence of redundant ocular signaling physiology, but it's likely that future approaches will focus on the mitigation of the retinal pathology that's the hallmark of open-angle glaucoma. Whatever the route to neuroprotection, this one-two punch of reduced IOP and diminished retinal cell loss is a goal that is in sight, and would be a major step forward in preserving visual function in patients with POAG. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School and senior clinical scientist at the Schepens Eye Research Institute. Dr. David is head of glaucoma, Mr. Shapiro is the vice-president of retina, and Dr. McLaughlin is a medical writer at Ora Inc.

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Surgery: Trending Towards the Tube

While both tube shunts and trabeculectomies have advantages, choosing between them may come down to surgeon preference.

Joseph F. Panarelli, MD, Miami

Surgery is seldom our first choice when treating a glaucoma patient. Medical and/or laser treatment are initially employed in most cases, in an effort to lower intraocular pressure. However, if the IOP remains elevated and the patient is still progressing or is deemed likely to progress, then we're faced with a decision about which surgery we should perform to keep the patient from losing more vision. That usually means choosing between a trabeculectomy and a tube shunt.

Is one a better choice than the other? Of course, to some extent the answer depends on the individual's circumstances. Studies of practice patterns in recent years have found a clear trend towards surgeons performing more tube shunts and fewer overall trabeculectomies, especially in eyes that have undergone previous surgery. Selection of tube shunts over trabeculectomy has increased from 7 percent to 46 percent in eyes that have undergone previous trabeculectomy and from 8 percent to 45 percent in eyes with prior cataract extraction.[1] A study by Pradeep Ramulu and colleagues, based on Medicare claims data, found that between 1995 and 2004 trabeculectomies in eyes without previous surgery or trauma dropped 51 percent, from 51,690 to 24,178 (although the number did increase 9 percent in eyes with scarring). During the same period, the number of tube shunts implanted increased 184 percent, from 2,728 to 7,744.[2]

Surgeons are clearly becoming more comfortable with the tube shunt option. They're no longer relegating tube shunts to the treatment of refractory glaucoma and patients at high risk of filtration failure.

The Evidence: Tube vs. Trab

In the first prospective, randomized trial of glaucoma drainage implants versus trabeculectomy, the Ahmed glaucoma valve and trabeculectomy for primary surgery were compared in 123 patients with average follow-up of 31 months.[3] The mean IOPs and adjunctive medications were comparable in the two groups. No statistically significant differences between groups were found for visual acuity, visual field or short- or long-term complications. (Differences in low-frequency complications would probably have been undetected in this study.) The cumulative probabilities of success were 68.1 percent for trabeculectomy and 69.8 percent for the Ahmed valve.

The Tube Versus Trabeculectomy study was a multicenter clinical trial that compared the 350-mm^2 Baerveldt glaucoma implant to trabeculectomy with mitomycin-C in patients who had undergone previous cataract extraction with intraocular lens implantation and/or failed filtering surgery. The five-year results showed that patients who underwent tube shunt surgery had a higher success rate than the trabeculectomy group; cumulative probability of failure was 29.8 percent in the tube group and 46.9 percent in the trabeculectomy group.[4] (Failure was defined as an IOP >21 mmHg or not reduced by 20 percent below baseline on two consecutive follow-up visits after three months; IOP <5 mmHg on two consecutive follow-up visits after three months; reoperation for glaucoma; or loss of light perception vision.)

In terms of IOP reduction, there was no statistically significant differ-

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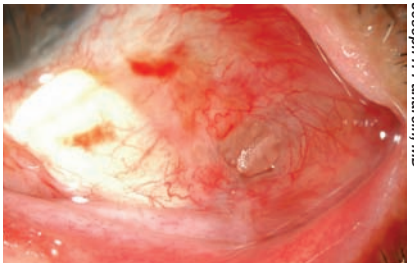
ence between the tube shunt group and trabeculectomy group. Both procedures produced a significant reduction in pressure that was sustained at the five-year follow-up, and there was a significant reduction in the use of supplemental medicines in both groups as well. Early postoperative complications were more frequently seen in the trabeculectomy group, though most were transient and self-limited. Late postoperative complications, reoperation for complications, vision loss and cataract extractions were not different between the two procedures. The one additional significant finding was that there was a higher rate of reoperation for glaucoma in the trabeculectomy group.[4,5]

Tube shunts have historically been used to treat refractory glaucomas—patients with advanced uveitic or neovascular glaucomas, or extensive conjunctival scarring, such as patients who've had multiple failed trabeculectomies. The inclusion criteria in the TVT study led to the implantation of tube shunts in patients at lower risk for surgical failure. What we can conclude from this study is that tube shunt surgery and trabeculectomy surgery will produce a similar reduction in IOP with a similar risk of serious complications in similar patient groups.

The Evidence: Caveats

It's important to critically review the results of the TVT study. There are three important points that should be addressed.

First, it's important to consider the specific reasons that a greater success rate was reported for the tube group than the trabeculectomy group. In both groups, the majority of patients failed because of inadequate pressure control—but there were also other reasons for treatment failure. In the trabeculectomy group, a handful of people did not meet the success requirements because their pressure was too low. In this study, the protocol called for a mitomycin-C concentration of 0.4 mg/ml to be placed for four minutes. Many surgeons use MMC for a shorter amount of time or use a lower concentration of MMC, and may have lower rates of hypotony as a result. The authors also point out that hypotony may be an acceptable outcome of surgery if visual acuity is not affected. (In any case, when the three patients with hypotony and stable vision were reclassified as successes instead of failures, the study results did not significantly change.)



Joseph F. Panarelli, MD

Plate exposure can be a surgical challenge. Often, these situations call for removal of the entire device, as conjunctival closure in this area can be difficult and recurrent erosions can occur.

Another major finding of the TVT study was that more patients in the trabeculectomy group had reoperations for glaucoma. This finding may have been skewed by the fact that surgeons have a greater comfort level doing a reoperation after a failed trabeculectomy (usually, putting in a tube shunt) than after a failed tube shunt. If a patient has an elevated IOP despite placement of one tube shunt, the surgeon may just increase medical therapy or observe a little longer before deciding to place a second tube shunt or perform a cyclodestructive procedure. On the other hand, it is important to note that in the TVT study there was no significant difference in mean IOP between treatment groups at the time of failure, in patients who had a reoperation for glaucoma or in patients who failed because of inadequate IOP reduction but did not have additional glaucoma surgery. These observations suggest that there was not a bias against reoperating for glaucoma in the tube group.

Finally, the study is limited by factors common to many large, multicenter, randomized clinical trials. Surgical outcomes can vary based upon the skill and level of experience of the clinicians involved in the study, and results cannot be generalized to different patient groups as this study enrolled patients who met very specific inclusion and exclusion criteria. Furthermore, low-frequency complications would have gone undetected (type II statistical error).

When I'd Choose a Tube

In my mind, there are three situations in which I would definitely choose a tube over a trabeculectomy.

• ***High-risk glaucoma patients.*** The first situation is when I'm treating secondary glaucoma patients at high risk of trabeculectomy failure. These are patients who have a history of neovascular glaucoma, uveitic glaucoma, iridocorneal endothelial syndrome, epithelial downgrowth or aphakic glaucoma. I find these glaucomas very difficult to control, and trabeculectomies have a high risk of failure in these patient populations. In my experience, a tube shunt is often the best surgery for these patients.

• ***Patients likely to need future surgery.*** When trabeculectomies work, patients and surgeons are happy, but when a bleb fails years later it can be disappointing. As we all know, additional surgeries performed on the eye create more inflammation and increase the risk of trabeculectomy failure. So, for example, I prefer to implant a tube shunt in any patient who has had a

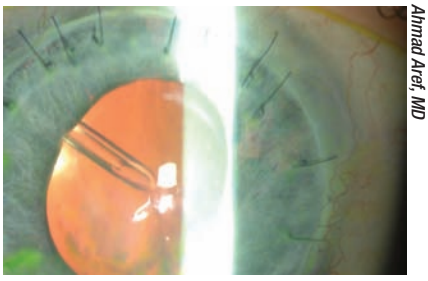
prior corneal transplant and needs IOP control. A trabeculectomy may initially work in these cases, but future surgeries for graft failure put the bleb at considerable risk. I have the same concern about patients who have serious diabetic retinopathy and may need retina surgery down the road.

• ***When follow-up is questionable***. When patient follow-up and compliance is a concern, I'd much rather place a tube shunt to control the glaucoma. I don't need to worry as much about these patients missing critical follow-up appointments in the early postoperative period—at least not as much as I would worry about a patient who's had a trabeculectomy. A trabeculectomy patient needs a lot of postoperative care in the first few weeks, and missing a few appointments can be devastating to the formation of a good bleb. Suture lysis performed too late is often ineffective, and noncompliance with medical therapy (i.e., anti-inflammatory treatment) can also result in early bleb failure.

Does Choice of Shunt Matter?

Data from the Ahmed Versus Baerveldt Study and the Ahmed Baerveldt Comparison Study suggests that there are pluses and minuses to the two most popular shunts we have at our disposal. The Ahmed implant is great because it gives you the benefit of immediate pressure reduction, and the valve minimizes the risk of hypotony. However, you have to deal with the fact that these tubes can become encapsulated, in which case their ability to adequately control IOP decreases over time.

One of the weaknesses of the Baerveldt shunt is that it is non-valved and hence needs to be occluded for the first few weeks after surgery. As a result, we don't always get an ideal pressure reduction right away, despite utilizing different techniques to fenestrate the tube. When the tube opens, there's also a higher risk of serious complications. Nevertheless, over the long run the Baerveldt seems to achieve slightly better pressure control (although the amount may not be clinically significant).



Ahmad Aref, MD

Patients with prior corneal transplants develop chronic angle-closure glaucoma and as a result can have shallow anterior chambers. Placement of a sulcus tube helps prevent long-term corneal endothelial damage.

The bottom line is that it's not yet clear whether one tube shunt is superior to the others. So for those opting to implant a tube shunt, the choice of device may come down to surgeon preference. Another factor is past experience; a bad experience with one device sometimes leads you to shy away from using it again in the future. A few cases of shallow anterior chambers with the Ahmed and you might switch to the Baerveldt. If you have some issues with hypotony after a Baerveldt opens, you might choose to switch to the Ahmed.

Ultimately, the results of comparative trials will have some impact on a surgeon's choice of implant device, but training and clinical experience will also play major roles.

When I'd Choose a Trab

On the other hand, there are patients for whom I prefer a trabeculectomy to a tube shunt:

• ***Patients with severe disease.*** If a patient has more severe glaucoma, I'm likely to aim for a lower target IOP. In that situation, I tend to prefer a trabeculectomy simply because I can get a very low pressure with this surgery. I think most practitioners feel that tube shunts are a good way to lower IOP and are very predictable, but they don't always get you a very low number. However, it was interesting to note that in the TVT study, the proportion of patients with an IOP ≤14 was similar between the two treatment groups. In fact, 63 percent of patients that underwent tube shunt surgery had an IOP less than 14.[4] Since this seems to contradict traditional thought, it's worth asking why. One possible explanation is that previous data has been skewed toward higher final pressures simply because in the past we've mostly implanted tube shunts in patients with refractory glaucomas who started out with very high pressures.

• ***Phakic patients—especially those with shallow anterior chambers.*** I would prefer a trabeculectomy in this situation because there is the risk of endothelial damage from putting a tube in too close to the cornea. Since the patient is phakic, sulcus placement is not an option. I feel that trabeculectomy is generally the preferred surgical option in phakic patients, but it will be interesting to see the results of the ongoing Primary Tube Versus Trabeculectomy Study. Although there is a trend towards more tube shunts being placed, the number of total trabeculectomies being done still significantly outnumbers the total of tube shunts being performed.

Other Considerations

Usually, a surgeon's three biggest fears with a tube shunt are tube erosion, endothelial damage and diplopia. The first two risks can be mitigated somewhat by the surgeon. For example, surgeons can decrease the risk of tube erosion by altering

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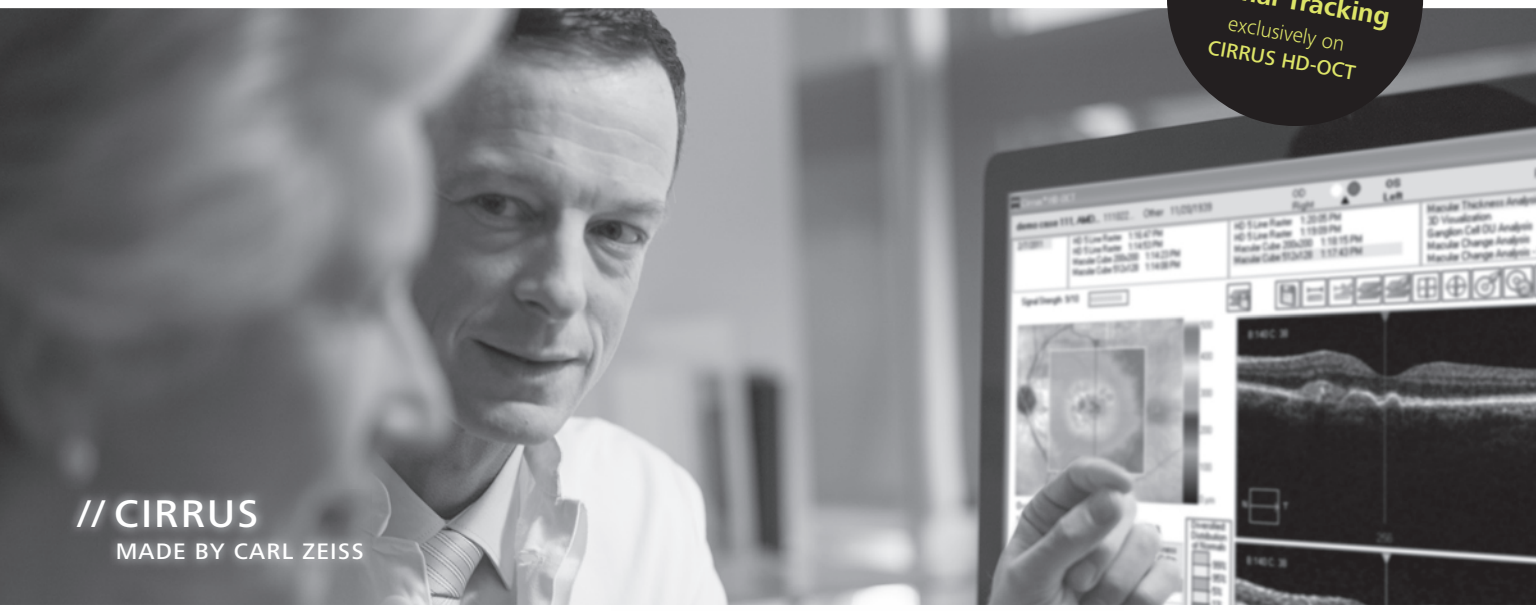

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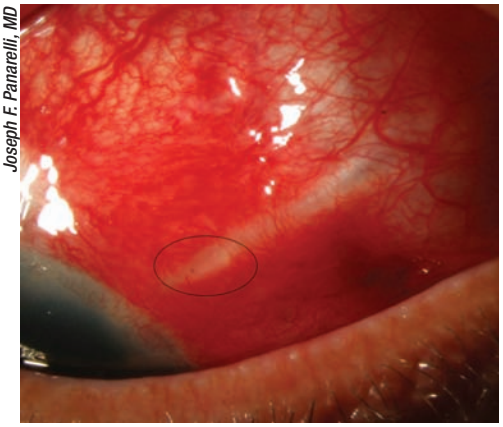
their technique a little bit. Tunneling the fistula tract a few millimeters prior to entering the anterior chamber and covering the tube adequately with a patch graft can help minimize exposure rates.

Unfortunately, we don't have great data regarding the effect tubes may have on the cornea, so most concerns about endothelial damage are based on anecdotal reports. One recent study looked at tube shunts after Ahmed implantation for refractory glaucoma, and it did find a reduction in corneal endothelial cells at two years of follow-up, with the greatest decrease in cell count in the quadrant of the tube's insertion.[6] However, another study found no difference in corneal decompensation rates when comparing pars plana tube placement to anterior chamber placement.[7]

Furthermore, trabeculectomy and other glaucoma procedures can also decrease corneal endothelial cell counts. One comparative study found no differences in graft failure rates after trabeculectomy with mitomycin-C vs. glaucoma drainage device implantation.[8,9] The PTVT study will compare endothelial cell counts in both trabeculectomy and tube shunt patients, and it will be interesting to look at the long-term results.

The third concern, diplopia, is a real risk in patients with the Baerveldt implant. The TVT study found that the risk of developing diplopia was about 5 percent.[4] Diplopia can be transient and often resolves within the first six months after surgery; if it persists, prisms can sometimes correct small deviations. However, there are times when patients ultimately need strabismus surgery for correction.

Minimizing diplopia is a challenge because there's not a lot we can do at this point. Diplopia is often related to the size of the bleb or the plate. To help decrease its incidence, about all we can do is make sure that our surgical technique does not disrupt or split the muscle fibers when implanting larger devices and ensure that the wings of the implant are completely beneath the proper muscle. Alternatively, we can choose an implant with a lower rate of strabismus postoperatively, such as the Ahmed glaucoma valve.[10]



Joseph F. Panarelli, MD

This patient developed a tube erosion and subsequent endophthalmitis, requiring a vitreous tap and injection of antibiotics along with explantation of the glaucoma drainage device.

Where Are We Headed?

I think it would be fair to say that when choosing between a trabeculectomy and a tube shunt for patients who have medically uncontrolled glaucoma, the best option is likely the one that you're most comfortable with. The data from the TVT study suggests that the risk profile and IOP reduction are very similar between the two groups. Neither surgery showed a clear superiority. We've already seen a shift in practice patterns, in that we're using tube shunts now for patients not only with refractory glaucoma but also those at lower risk for filtration failure. The question is, what role will tube shunts play for patients with mild or newly diagnosed glaucoma, or patients that have not had previous intraocular surgery? And, of course, new drainage devices are in the pipeline; how they will influence surgeons' choices remains to be seen.

Minimally invasive glaucoma surgeries such as Trabectome, canaloplasty and the iStent are also gaining popularity. However, like any new procedure, these have a learning curve. Furthermore, these procedures may be better suited to treating mild-to-moderate glaucoma rather than more advanced disease. For patients with more severe glaucoma, I think a tube shunt or trabeculectomy remains the better choice; they produce a more significant reduction in IOP and help keep the patient from suffering additional visual field loss.

Many surgeons feel very strongly about whether a tube shunt or a trabeculectomy is more effective. You can make good arguments on either side, but what matters most is that both options work well. REVIEW

Dr. Panarelli is an assistant professor of ophthalmology at Bascom Palmer Eye Institute in Miami.

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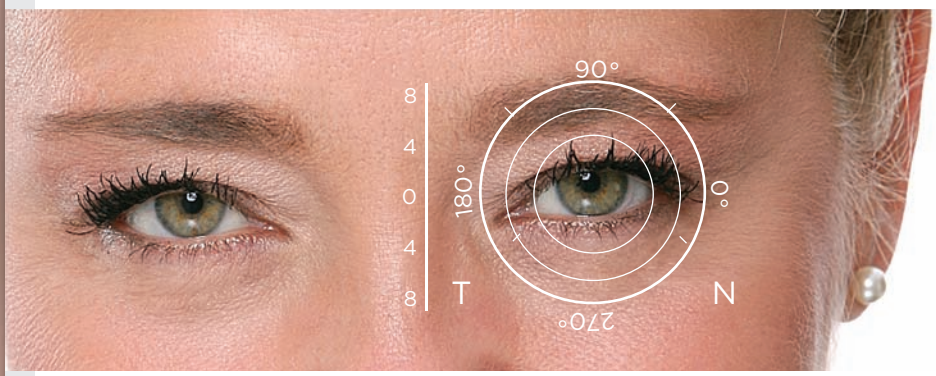

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Refractive Surgery Is Good to Go

A look at how refractive surgery is handled in the military, and the regulations even a civilian surgeon needs to be aware of.

Walter Bethke, Managing Editor

The phrase "good to go" has worked its way into everyday speech, but its roots are actually in the military, where it denoted that an individual or group was mission-ready. Though the military initially took a skeptical view of refractive surgery for its soldiers and seamen, procedures such as PRK and LASIK are now good to go and mission-ready themselves, and can often allow soldiers to operate more effectively without the need for vision correction. Refractive surgery isn't suitable in all cases though, and there are rules governing it that refractive surgeons need to be aware of, since some of their patients may want or need refractive surgery in order to enlist. Here's what you need to know.

Vision Requirements

In general, the Department of Defense will disallow anyone who isn't correctable with spectacles to one of the following: 20/40 in one eye and 20/70 in the other; 20/30 in one and 20/100 in the other or 20/20 in one eye and 20/400 in the other.[1] However, refractive surgery starts to enter the discussion because particular occupations have more stringent requirements. For example, individuals with flight status or those in the elite special forces must be correctable to 20/20. "This gets to the premise for performing refractive surgery in the armed forces, specifically in aviators," says David Tanzer, MD, an ophthalmologist in San Diego and a retired Navy flight surgeon who has either directed or participated in several landmark military refractive surgery studies. "It's because the environmental stresses those warriors face make the wearing of contact lenses and/or glasses much more difficult. For an aviator, G-forces will pull spectacles down off the nose and contact lenses have been shown to occasionally become displaced in an aviation environment. Also, for a special operator, having his glasses broken or developing microbial keratitis from contact lens wear would make him a casualty, unable to do his job and a danger to his team."

Dr. Tanzer says that for the best chance at a good result, surgeons should use the latest technology. "If at all possible, I'd strongly encourage any civilian surgeon who is performing refractive surgery on a candidate who wants to join the military to use wavefront-guided or wavefront-optimized ablation profiles," he says. "Conventional profiles should be avoided because of the known issues regarding induced aberrations, specifically spherical aberration. And, if someone elects to perform LASIK, create the flap with a femtosecond laser, preferably with one that allows a reverse-bevel side cut, which has been shown to be stronger than an externally angulated side cut."[2,3]

Refractive Regulations

The military makes free refractive surgery available to all its members, but there is a wait list in which certain occupations get priority. In the Navy, for example, those on flight status or dive status (i.e., special forces) are at the top. Because of this and for logistical reasons, there are many warriors who aren't able to receive refractive surgery in a timely fashion. "So individuals will seek us out, the civilian refractive surgeon," says Dr. Tanzer. "They may have a deployment coming in three to six months, and they've been told their name might not reach

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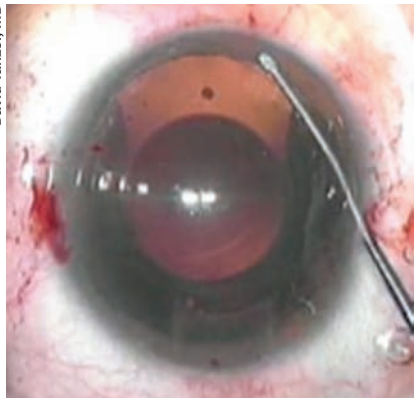
the top of the surgery list for another nine to 12 months. However, they don't want to make their deployment—often their second, third or fourth—wearing glasses or contact lenses." Dr. Tanzer notes that designated personnel on flight status in the Navy must receive their refractive surgery at a Navy refractive surgery center but anyone else on active duty can have surgery by a civilian surgeon, provided they have received permission from their commanding officer.

Dr. Tanzer says he sees a number of people who want to join the military but need better vision to be able to get the occupation they want. It's with these patients the civilian surgeon needs to be especially careful, since there are rules regarding what surgeries can be done. Specifically, any incisional refractive surgery, such as corneal transplants, RK, AK or corneal implants will disqualify the applicant, as will refractive lens exchange or pseudophakic status in general (though Dr. Tanzer believes pseudophakia might be handled on a case-by-case basis). Also, even though laser refractive surgery such as PRK and LASIK are allowed, the military retains the right to disqualify a post-refractive patient for a number of reasons, and all the information regarding the procedure has to be presented upon the candidate's military physical exam.

"A college senior came into my office who wanted to be a naval aviator and he felt refractive surgery could help him achieve that," recalls Dr. Tanzer. "His refractive error, however, was -9.5 D, and I had to be the bearer of bad news, telling him that not only is his error outside the accepted parameters for being a naval aviator regardless of surgery, but he can't even join the service: No one can have a refractive error outside of ±8 D." Additionally, pre-surgical astigmatism can't exceed 3 D. Navy regulations require that there be at least 12 months between the last procedure and the candidate's physical to allow the eyes to stabilize (a time interval that varies by branch of service), and there must not have been any complications or interventions as a result of the surgery.



David Tanzer, MD

Candidates for military service may receive a Visian ICL with proper permission.

It's also crucial for the civilian eye surgeon to know that some procedures are allowed only if the candidate gets a waiver beforehand. "I saw another young man in my office three months ago," says Dr. Tanzer, "He was a senior going to a local college on the Navy ROTC scholarship, and his dream was to become an [explosive ordnance disposal] officer. To achieve that, though, you can't wear contact lenses. As a -7 D myope, he was surveying his options with regard to refractive surgery in order to be free of contact lenses for the EOD officer training. Unfortunately, his workup showed that his corneas were 460 µm thick.

"I explained to him, though, that he could have an ICL," Dr. Tanzer continues. "The problem is that phakic IOLs aren't allowed for someone who is not already on active duty, which he technically wasn't. I told him if I were to implant ICLs, the Navy would have the option to essentially kick him out of the program. I recommended he discuss it with his recruiter and request a waiver so we could consider the ICLs. A month later, he completed the waiver process, received permission, and we performed bilateral, simultaneous ICL surgery on him. He had a great result. He was 20/15 uncorrected in each eye on day one postop and with a perfect vault between the ICL and the crystalline lens. He's been accepted for entrance into the EOD officer training program upon graduation. Words can't describe how good I felt."

In the military, lens surgery is approached a bit differently. "The caveat is anyone on flight status," he says. "If an aviator has a lens-based procedure, multifocal IOLs are not allowed because of the known decrease in contrast acuity and the potential for glare and halo." He did, however, successfully implant an aspheric accommodating monofocal lens in a Navy SEAL who had developed a visually significant cataract. Dr. Tanzer says he recently ran into this patient and he reported his eyes were still doing great. "This is yet another example of our ability to take the outstanding technology available to us as ophthalmologists and use it appropriately in these motivated individuals to keep them doing what they are trained to do," Dr. Tanzer says. "I derive a tremendous amount of satisfaction in being able to do that as a civilian surgeon."

The work military researchers have done on LASIK is making its way to physicians in general, and a large-scale LASIK study Dr. Tanzer performed while in the service is being considered for publication. "The study shows what I consider to be the best results I've seen published demonstrating the safety and effectiveness of wavefront-guided LASIK with a femtosecond flap," he says. "And it was based on those results that LASIK is now allowed as a routine procedure on someone in the Navy on flight status." REVIEW

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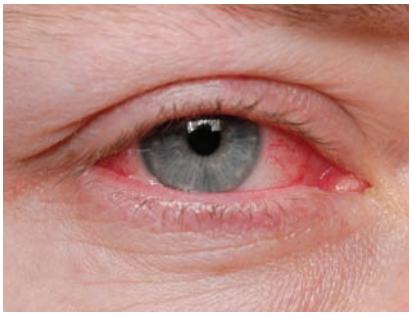
A Correlation Between Migraines and Dry Eye

An observational comparative study of 33 migraine sufferers who were referred from a neurology clinic and 33 control subjects who were referred from an ophthalmology outpatient clinic found that an increased frequency of dry-eye disease might be related to migraine headaches. The control subjects had neither systemic nor ocular disease nor any type of headache. All 66 patients underwent a complete ophthalmic examination and diagnostic tests for dry eye, including tear breakup time, Schirmer test with topical anesthesia, lissamine green staining and an ocular surface disease score. Patients with migraine were classified as migraine with aura (n=17, 53 percent), migraine without aura (n=11, 33 percent) and basilar migraine (n=5, 15 percent); a pain score from one to four was determined for each patient based on the American Headache Society's Migraine Disability Assessment Test.

Significant differences in dry eye scores were found between the patients with migraine and the control subjects. In the migraine group, the mean tear breakup time was 7.75 ±2.37 seconds, whereas in the control group it was 9.15 ±1.93 seconds. For the Schirmer test, the migraine group had a mean value of 12.09 ±4.95 mm/5 minutes, whereas the control group had a mean value of



Patients with migraine may suffer from dry eye more than those without migraine attacks.

14.90 ±4.26 mm/5 minutes. Testing with lissamine green staining resulted in a mean value of 1.00 ±0.16 in the migraine group and 0.30 ±0.46 in the control group. In the migraine group, the mean for the ocular surface disease index scoring was 36.27 ±17.54. In the control group, it was 28.42 ±9.0. A significant difference ($p<0.05$) was found in the dry-eye syndrome testing results between the two groups in the study.

Cornea 2012;31:1414-146

Koktekir B, Celik G, Karalezli A, Kal A.

Topical Cyclosporine Improves Tear Film Stability in MGD

Researchers from Bangkok ran a three-month, randomized and double-masked clinical trial comparing the efficacy of topical cyclosporine [0.05% cyclosporine A (CsA)] and preservative-free artificial tears in the treatment of meibomian gland dysfunction, concluding that topical CsA 0.05% twice daily may help treat MGD by improving tear-film stability.

Patients (n=70) with symptomatic MGD and unstable tear film (tear-film breakup time <8 seconds) were randomized to a topical CsA (0.05%, group A) and 0.5% carboxymethylcellulose (control, group B) instilled twice daily for three months. Ocular Surface Disease Index (OSDI); lid margin inflammation; meibomian gland expression; conjunctival injection; corneal and interpalpebral dye staining; and noninvasive tear breakup time (NIBUT) using the Tearscope Plus and invasive fluorescein tear breakup time (FBUT) and Schirmer I test were performed.

At the three-month evaluation, mean OSDI, NIBUT and FBUT; lid margin inflammation; meibomian gland expressibility; and tarsal injection showed significant improvement from baseline in group A ($p<0.01$, $p<0.01$, $p<0.001$ and $p<0.001$). In group B, only the OSDI improved significantly from baseline at three months ($p=0.003$). TBTs (NIBUT and FBUT) were significantly longer in group A at all visits, and the mean change of TBUTs was also significantly greater in group A at three months ($p<0.001$).

Cornea 2012;31:1386-1393

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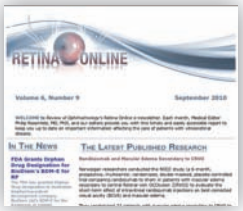

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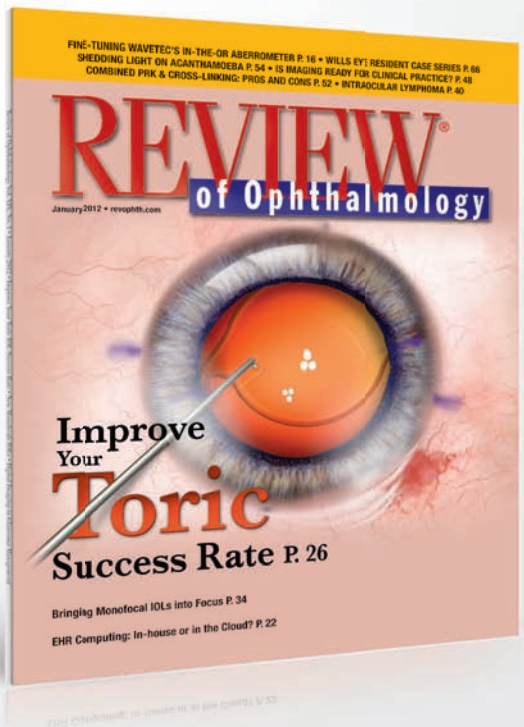

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LUMIGAN® 0.01% AND 0.03%
(bimatoprost ophthalmic solution)

Brief Summary—Please see the LUMIGAN® 0.01% and 0.03% package insert for full Prescribing Information.

INDICATIONS AND USAGE

LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Pigmentation: Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes: LUMIGAN® 0.01% and 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: LUMIGAN® 0.01% and 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% and 0.03% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory, or Neovascular Glaucoma: LUMIGAN® 0.01% and 0.03% has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

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

Use With Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and 0.03% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

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

In clinical studies with bimatoprost ophthalmic solutions (0.01% or 0.03%) the most common adverse reaction was conjunctival hyperemia (range 25%–45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common reactions (>10%) included growth of eyelashes, and ocular pruritus.

Additional ocular adverse reactions (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis, was reported in less than 1% of patients.

Systemic adverse reactions reported in approximately 10% of patients with bimatoprost ophthalmic solutions were infections (primarily colds and upper respiratory tract infections). Other systemic adverse reactions (reported in 1 to 5% of patients) included headaches, abnormal liver function tests, and asthenia.

Postmarketing Experience: The following reactions have been identified during postmarketing use of **LUMIGAN®** 0.01% and 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **LUMIGAN®** or a combination of these factors, include: dizziness, eyelid edema, hypertension, nausea, and periorbital and lid changes associated with a deepening of the eyelid sulcus.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether **LUMIGAN®** 0.01% and 0.03% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** is administered to a nursing woman.

Pediatric Use: Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

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

Hepatic Impairment: In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.03% for a 10 kg child.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

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

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

PATIENT COUNSELING INFORMATION

Potential for Pigmentation: Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution).

Potential for Eyelash Changes: Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01% and 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice: Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN®** 0.01% and 0.03%.

Use with Contact Lenses: Patients should be advised that **LUMIGAN®** 0.01% and 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs: Patients should be advised that if more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

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

Diagnosis, Workup and Treatment

The patient underwent B-scan ultrasonography of the left eye, which excluded scleral thinning or associated orbital involvement. Soon thereafter he was taken to the operating room for excision of the involved area of conjunctiva and lower lid nodule, as well as exploration of the anterior orbit and inferior rectus muscle. A vascularized, infiltrative process that involved the conjunctiva and Tenon capsule and extended into the capsule of the inferior rectus muscle was noted. The underlying sclera appeared grossly normal and was not resected. The process spared the intraconal space. The affected areas were excised and debrided and the eyelid lesion was excised externally. Reconstruction was not done to maximize the effectiveness of topical therapy. Cultures for aerobic, anaerobic, fungal and acid fast bacilli (AFB) were obtained. Formalin-fixed tissue was submitted for histopathologic evaluation.

Postoperatively, the patient was empirically placed on bacitracin/polymyxin B ointment, fortified cefazolin and tobramycin drops, and oral clarithromycin. On postoperative day two, histopathology demonstrated foci of granulomatous inflammation encompassing microabscesses in the conjunctiva and skin. Special stains disclosed numerous AFB within vacuoles within the inflamed conjunctival tissue *(See Figures 2 & 3)*. As a result, fortified amikacin and gatifloxacin drops were administered. Two weeks later, one of three anaerobic cultures was positive for "very light AFB," and one of three AFB cultures was positive for atypical mycobacteria without speciation. Fungal cultures were negative. A reference laboratory identified the pathogen as *Mycobacteria chelonae*, resistant only to ciprofloxacin and doxycycline. Over the next two weeks, the patient's clinical appearance improved dramatically. Oral and topical treatment has continued 12 weeks postoperatively, with no evidence of recurrent infection.

Both images: Ralph Eagle, MD

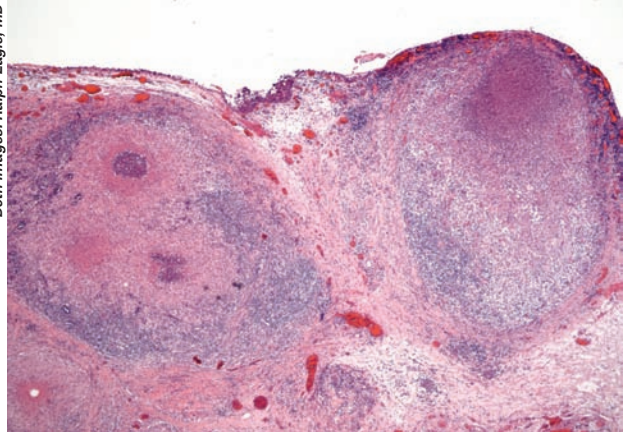

Figure 2. Histopathology of a conjunctival tissue sample demonstrating two well-circumscribed granulomas.

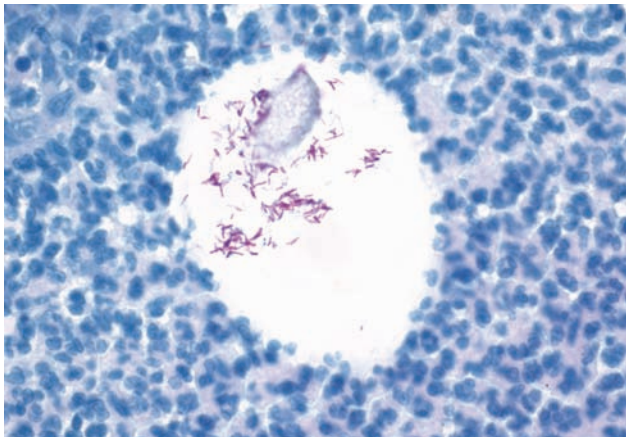

Figure 3. Acid fast staining of conjunctival tissue demonstrating multiple organisms within a vacuole.

Discussion

Although it remains relatively rare, non-tuberculous or "atypical" mycobacteria (NTM) have become increasingly significant ocular pathogens during the past few decades. Ramana S. Moorthy and colleagues reviewed clinically significant NTM and compiled more than 200 case reports of ocular and adnexal NTM infections.[1] NTM phenotypically are classified into four categories, known as Runyon Groups, based on their ability to produce pigment and their rate of growth in culture. Group IV, "rapid growers" that do not produce pigment, cause most ocular and adnexal NTM infections and include *M. chelonae*, *M. abscessus* and *M. fortuitum*.

Reflecting their rarity, there are no clear guidelines for treatment of ocular and ocular adnexal infections caused by NTM. Only two cases of conjunctival NTM infection have been reported previously in the literature,

and both were associated with prior ocular surgery. The first was a case of conjunctivitis and scleritis caused by *M. chelonae* following vitrectomy.[2] The infected eye ultimately was enucleated despite four weeks of intravenous amikacin, imipenem and vancomycin in addition to oral clarithromycin and topical amikacin. The second case was an isolated conjunctivitis culture-positive for M. abscessus following scleral tunnel incision and phacoemulsification.[3] The patient recovered after 15 weeks of therapy with oral clarithromycin, ethambutol, rifampicin, and ciprofloxacin and topical ciprofloxacin. In both cases, diagnosis was significantly delayed because initial conjunctival swab cultures were negative, necessitating conjunctival excision for biopsy and culture. The organisms in both patients also were resistant to initial topical antibiotics, reflecting NTM's frequent resistance to clarithromycin and amikacin. Based on this admittedly limited anecdotal data, at least one month of systemic intravenous antibiotics (amikacin, imipenem or vancomycin) and topical amikacin are recommended therapy for isolated NTM conjunctivitis.[1]

When considering the pathogenesis of our patient's infection, it should be noted that, in contrast to the aforementioned cases of NTM conjunctivitis, the postop infection reported here was not localized to the region of initial surgical incisions. It is possible that the patient's conjunctiva may have been colonized with mycobacteria prior to surgery, or he could have acquired the infection postoperatively via contaminated water.[4] Given a number of reports regarding bacterial contamination of multiple use vials,[5,6,7] it is also conceivable that the offending pathogen was iatrogenically introduced when peribulbar anesthetic was administered intraoperatively and tracked along anatomic planes within the conjunctiva and Tenon fascia. However, no similar postop infections developed in other patients treated in the same operating room who received injections from the same vials of anesthetic. Although intraoperative use of mitomycin for pterygium excision has been linked to an increased risk of postoperative infections,[8] it is unlikely to have played a role in this case because the mitomycin was applied nasally and the infection arose inferotemporally. Even more confounding is the involvement of the patient's isolated left lower lid nodule, given its distance from the site of surgical manipulation.

The key to timely, accurate diagnosis of NTM is a high level of clinical suspicion preoperatively, which assures that appropriate microbiological cultures and special histopathological stains for AFB and fungi will be performed. In this case, the indolent, relatively painless course with the appearance of multiple nodules alerted the treating physicians of the possibility of AFB infection. REVIEW

The author would like to thank Jurij R Bilyk, MD, of the Oculoplastic and Orbital Surgery Service, Irving Raber, MD, of the Cornea and External Disease Service and Ralph C. Eagle Jr., MD, of the Department of Pathology for their time and assistance in preparing this case report.

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REVIEW

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Despite successful pterygium excision, a conjunctival elevation prompts referral to Wills' Oculoplastic and Orbital Surgery Services.

Murtaza Adam, MD

Presentation

A 57-year-old Hispanic male was followed by the Wills Eye Institute Cornea Service for six weeks following excision of a recurrent nasal pterygium with mitomycin and a superior conjunctival autograft. Although the area of pterygium excision was healing well, a multinodular area of elevation of the inferior and lateral conjunctiva had developed, extending into the inferior cul-de-sac. Treatment with oral cephalexin and topical neomycin/polymyxin B/dexamethasone was immediately initiated, but this did not ameliorate the patient's conjunctival findings or associated symptoms of mild eye discomfort and foreign body sensation. After five weeks of presumptive therapy, the patient admitted that he never filled his prescription for cephalexin and had discontinued topical treatment a few weeks earlier. He subsequently was referred to the Oculoplastic and Orbital Surgery Service eleven weeks postoperatively for further management. The patient denied pain, diplopia or changes in visual acuity..

Medical History

The patient's past ocular history was significant for recurrent pterygium following initial excision in both eyes 30 years previously and twice more in the left eye. His past medical history was significant for coronary artery disease, hypertension, hyperlipidemia, type 2 diabetes (well controlled), gastroesophageal reflux and asthma. His medications included clopidogrel, aspirin, multiple anti-hypertensives, a beta blocker, insulin, two oral hypoglycemics, albuterol and a proton pump inhibitor. He denied any recent travel and had no pets at home. Social history was negative for high-risk sexual activity or alcohol, tobacco and recreational drug use.

Examination

The patient's uncorrected visual acuity was 20/50 in the right eye and 20/60 in the left. Pupils were normal with no afferent pupillary defect. Motility was full on the right and diminished approximately 20 percent in all ductions except adduction on the left. He denied diplopia in all directions of gaze. Intraocular pressure was within normal range and equal in both eyes. There was no proptosis. No preauricular lymphadenopathy was appreciated. The patient had an isolated, non-tender, raised, erythematous nodule on his left lower lid. The anterior exam of his left eye was significant for marked conjunctival injection with nodularity extending inferotemporally (See Figure 1). The surgical site (nasal conjunctiva) appeared benign and there was no corneal staining or infiltrate. Nuclear sclerotic lens changes were present. His funduscopic exam was normal in both eyes.

Figure 1. Inferotemporal conjunctival injection and nodularity of the left eye.

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

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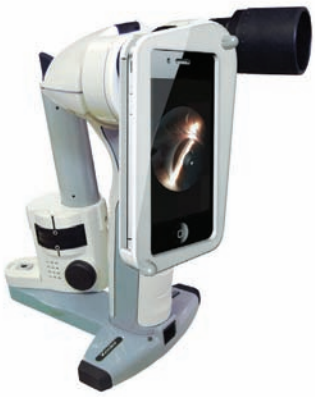

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Important Safety Information

Warnings and Precautions: LUMIGAN® causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

LUMIGAN® should be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported with LUMIGAN®. LUMIGAN® should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Adverse Reactions: The most common (25%-45%) adverse event with LUMIGAN® was conjunctival hyperemia. Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia. Other common events (> 10%) included growth of eyelashes and ocular pruritus.

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

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