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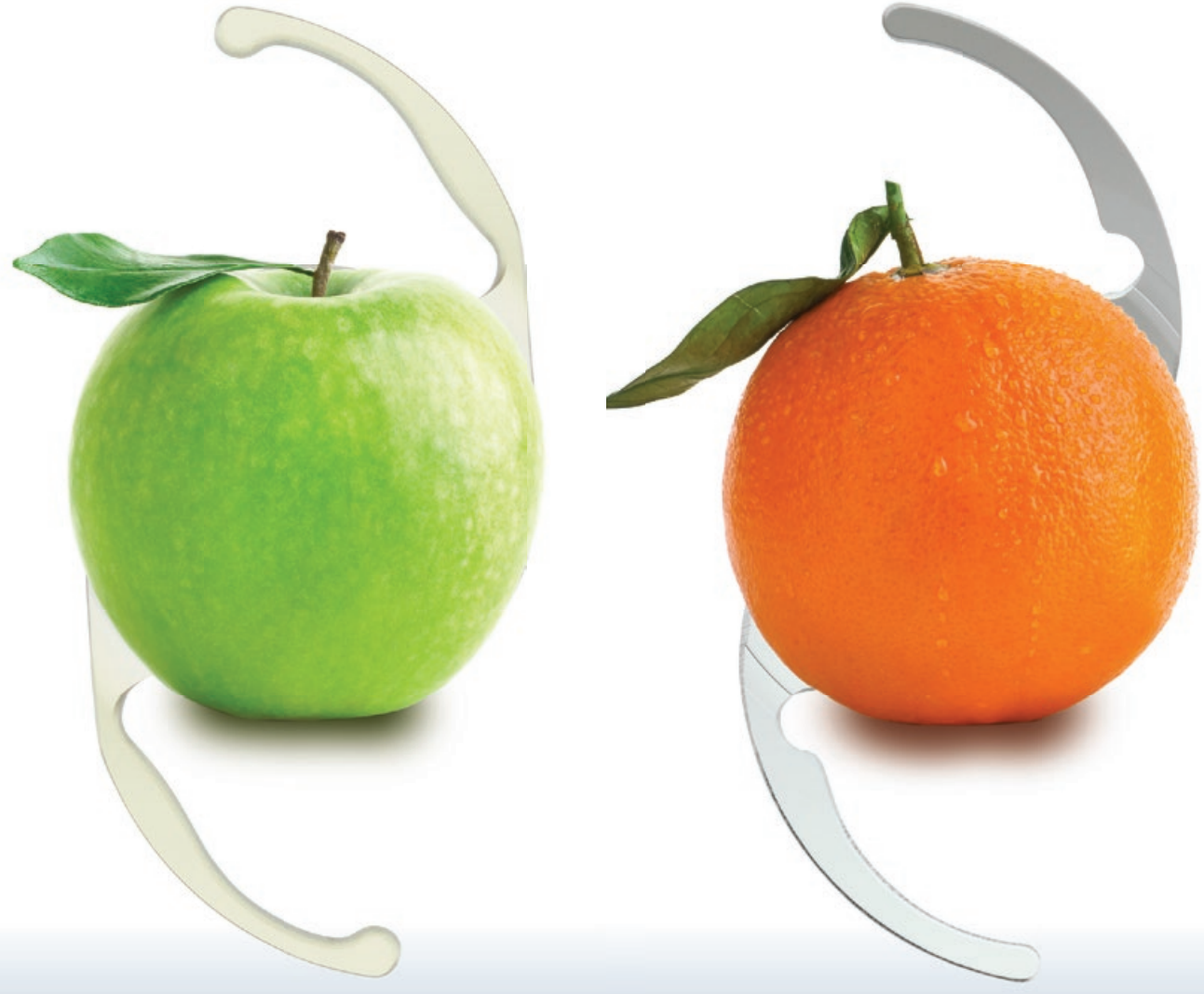

1. Lee BS, Chang DF. Comparison of the rotational stability of two toric intraocular lenses in 1273 consecutive eyes. *Ophthalmology*. 2018;0:1-7.
2. Potvin R, et al. Toric intraoclar lens orientation and residual refractive astigmatism: an analysis. *Clin Ophthalmol*. 2016;10:1829-1836.

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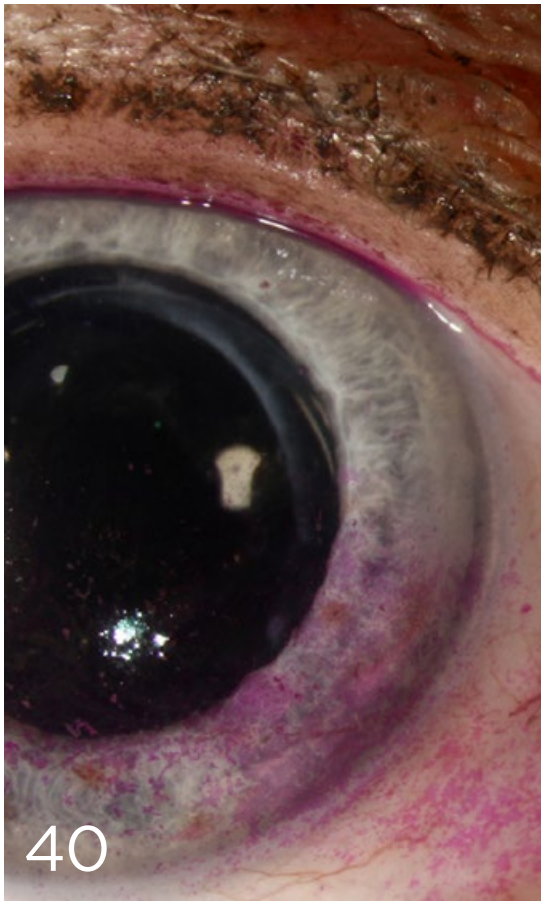

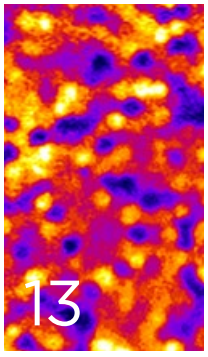

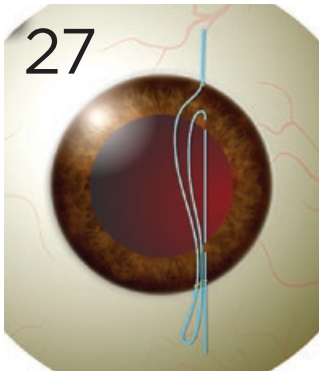

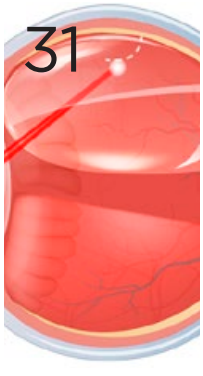

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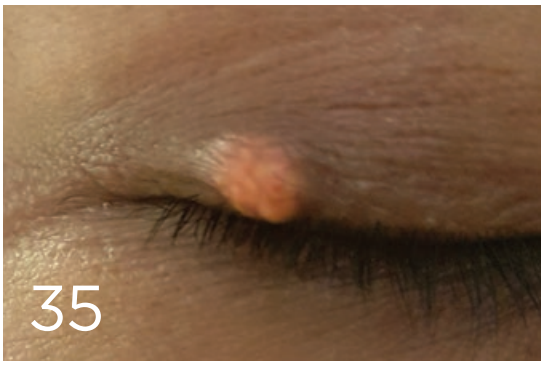

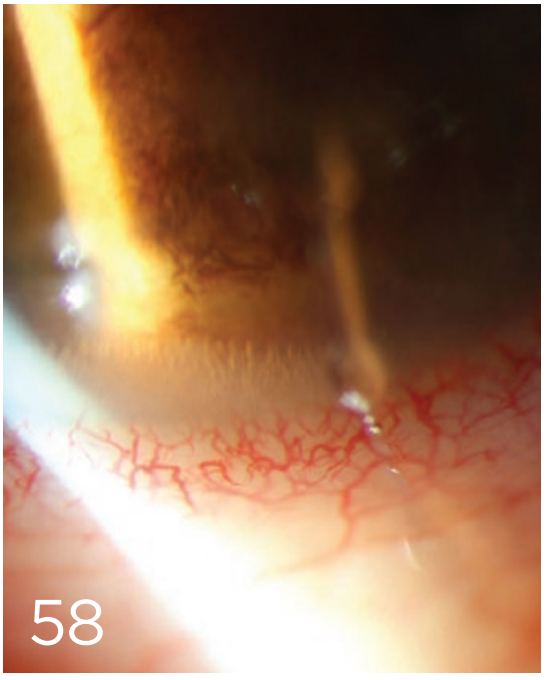

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Opinion

RUTH D. WILLIAMS, MD

Is Burnout a Symptom of Moral Injury?

I spent several hours last year at a CME event required by our hospital system. The topic was physician burnout, and a midlevel mental health provider gave a lecture on how to take care of ourselves. She suggested that we practice meditation, exercise regularly, eat healthy foods, spend more time with family, and take mini-breaks during the work day. One of my partners across the room texted me, "I could be doing some of those things if they didn't require me to be sitting here all evening." It seemed that the system was part of the problem.

In a widely quoted piece, Simon Talbot and Wendy Dean explained why physicians like me don't appreciate advice on how to manage work stressors. They wrote, "The concept of burnout resonates poorly with physicians: It suggests a failure of resourcefulness and resilience, traits that most physicians have finely honed during decades of intense training and demanding work."[1] Advice about how to combat burnout feels condescending. Even worse, it suggests that the physicians are somehow responsible for the problem.

Talbot and Dean suggested that burnout isn't the issue. Instead, they argued, it is a symptom of a larger problem they describe as "moral injury," which arises from a conflict of values. Moral injury—which is similar to post-traumatic stress disorder—was initially described in war veterans, and it results from "perpetrating, failing to prevent, or bearing witness to acts that transgress deeply held moral beliefs."[2]

As for physicians, we took an oath to put the needs of our patients first, yet we face competing demands from an increasingly profit-driven and complex system. Insurance companies, pharmacies, pharmacy benefit managers, private equity firms, and pharmaceutical and device companies strive to enhance quarterly profits. We work within this system for the interests of the individual patient, and this puts the ophthalmologist in the center of a conflict.

Could this conflict cause moral injury in physicians? I thought of some examples which suggest that it does.

Shortly after my practice implemented Epic, I developed neck and back pain from craning to look at patients. But could the real issue be something deeper than my physical symptoms—and the solution more profound than the need for a massage or a scribe or a tablet? Ophthalmologists observe the facial expressions and body movements of the patient sitting in the exam chair. However, the emergence of EHRs has diverted our thoughts from the patient to the screen. Is it possible that EHRs are competing for our attention and that the patient is no longer our primary concern? Could this cause a moral injury?

One of my patients has a worrisome visual field, and I recommended magnetic resonance imaging of the brain and orbit. However, he can't afford the test. Does the hospital system charge too much for the MRI? Is the insurance plan shifting too much cost to the patient? What if he has a tumor and can't afford additional testing or treatment? What is my malpractice risk if no MRI happens? It's my job to negotiate a solution for this patient, and I worry about him when I'm at home. Perhaps, as Talbot and Dean wrote, "Navigating an ethical path among such intensely competing drivers is emotionally and morally exhausting."

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Perhaps moral injury develops from the steady accumulation of conflicts like these. And while wellness strategies may address some symptoms of burnout, they won't solve the problem of moral injury.

Let's expand the conversation about physician burnout to include specific dysfunction in the health care system. Instead of leaning heavily on "physician, heal thyself," let's also discuss ideas about how to protect the physician/patient relationship. (One example is the Academy's push to end prior–authorization abuses by Medicare Advantage plans.) Working together on a common goal contributes to moral healing.

1 www.statnews.com/2018/07/26/physicians-not-burning-out-they-are-suffering-moral-injury.

2 Litz BT et al. *Clin Psychol Rev.* 2009;29(8):695-706.

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Current Perspective

DAVID W. PARKE II, MD

Medical Record Ownership and Access

In the days of paper and pen, medical records were tangible documents. Most physicians considered that they owned the file cabinet in which records were stored and the physical documents within. Patients could obtain copies of the record with due authorization. Transfer of practice ownership often came with patients' records, and this seemed to confirm that the records were an asset of the practice.

Well, what about now—in the era of electronic health records (EHRs)? Today's file cabinet is represented by the architecture of the EHR, and the physical record exists as invisible digital data bytes. Who should own the record? Who should control access to the record? It's not a clear area legally, ethically, or operationally.

The Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rules gives patients certain rights with respect to their medical records. HIPAA says that a patient is allowed to "inspect, review, and receive a copy of his or her medical records" held by all providers covered under HIPAA. Individual states have long had laws pertaining to protection, maintenance, copying, and disposal of records. But while some states provide that a physician or health system employer owns the medical record, most state laws are silent about actual ownership of the physical record. Only New Hampshire provides definitively that medical record patient-specific information is owned by the patient. (However, multiple surveys indicate that generally about half of all patients believe they own their medical records.)

The issue of who *should* own the records—physician or patient—is complex, replete with questions around health literacy, potential for patient confusion, and even misinterpretation of the old-fashioned Shortness Of Breath acronym. However, most physicians are comfortable with the concept that patients should be able to access their entire medical record upon request. Many EHRs now contain patient portals providing varying degrees of data access.

Control of record access is different from simple ownership. EHRs have created new challenges including access issues derived from the sharing of a single record among multiple specialties, protocols for destruction of EHR notes that are past the statute of limitations for legal action, etc.

Another HIPAA issue concerns differential access to potentially patient-identifying data or protected health information (PHI) versus de-identified data. Data containing PHI are frequently accessed under HIPAA by health systems and payers for quality of care, payment, and business operations. (As an example, patients with certain risk factors may be robocalled, with the messages prompting them to "ask your doctor about statins" or offering tools for blood sugar control.) They may not be accessed by third parties beyond these permitted exceptional uses.

David W. Parke II, MD
Academy CEO

De-identified aggregated data (not containing PHI) may be accessed for a variety of desirable purposes, such as infectious disease community surveillance, FDA postmarketing approval studies, population health research, and quality improvement.

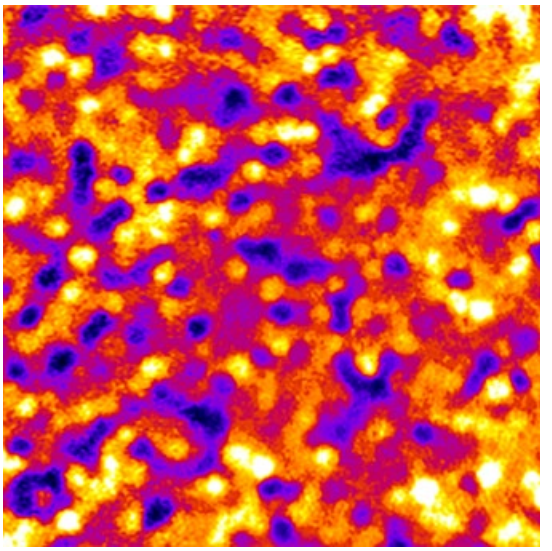
EHR clinical data are even making their way into the world of social media. Last year, Facebook tried to acquire de-identified patient records to match them with identifiable Facebook user data—and create digital health profiles. HIPAA does not prevent this. Consider the privacy implications.

The physician's conundrum becomes even more complex when the EHR vendor contractually retains exclusive use of de-identified data and doesn't make it available for socially and medically desirable purposes. This is analogous to saying to the physician, "You own the data contained in the file, but you can't open the file." Ownership then becomes a moot point.

Some policymakers believe that the solution is clear patient ownership of health data with assignment of access rights to physicians and facilities as needed. In the meantime, it behooves us all to pay attention to data rights, both as physicians and as patients. It's a confusing topic with parties other than the physician and patient involved, a fuzzy legal environment, and the potential for unforeseen and potentially undesirable outcomes.

News in Review

COMMENTARY AND PERSPECTIVE



IN SITU. *NEI scientists have visualized and tracked the mosaicism of RPE cells (shown here).*

Johnny Tam, PhD, NEI

RETINA

RPE Deterioration Tracked With Adaptive Optics

A SPECIALIZED IMAGING SYSTEM developed at the NEI can directly visualize deterioration of the retinal pigment epithelium (RPE) over time—an achievement that is enabling the researchers to begin investigating the system's utility for directly tracking the progression of blinding retinal diseases.

"We've only recently started to apply this technique to investigate diseases," said study leader Johnny Tam, PhD, at the NEI. "Currently we're interested in seeing how RPE cells are affected in diseases such as age-related macular degeneration as well as various inherited retinal degenerations."

How it works. The imaging system combines adaptive optics (AO) with indocyanine green (ICG) angiography and scanning laser ophthalmoscopy to produce detailed structural images of the photoreceptor-RPE-choriocapillaris complex in living human eyes.[1] (See "News in Review," February.)

Focusing on the RPE. In their most recent study, the researchers concentrated their attention on the RPE. They injected ICG dye in healthy subjects with visual acuity of 20/20 or better and in patients with two types of progressive hereditary degenerative retinal diseases—late-onset retinal degeneration (L-ORD) and Bietti crystalline dystrophy (BCD).

The images from ICG injections taken months apart showed that the system could track changes in the RPE, the researchers found.[2] The RPE cell mosaic was stable in the healthy eyes, was slightly less stable in L-ORD, and changed drastically in BCD.

"This study is a step toward functional imaging of RPE cells, in which we start to explore the dynamics of dye uptake and clearance across a large range of time—seconds to a year," Dr. Tam said. "We believe that imaging the RPE, in combination with other clinical assessments, will allow us to identify patients who are at risk for losing their vision."

Long-term goal. The research group's long-term goal is to bring the lessons from its adaptive optics system into widespread clinical use, Dr. Tam said. As part of this, the researchers noted that they observed a characteristic AO-ICG fluorescence pattern in every healthy eye that they imaged, and they are using this information to create an in vivo database of human foveal RPE cell-to-cell spacing.[2]

"Translating this technique to a standardized clinical test is a tremendous endeavor, but we have achieved a critical first step by deploying our custom-built instrument in a clinical setting at the NEI's Eye Clinic," Dr. Tam said.

"In the past decade we've witnessed rapid advances in technology, and it would not be inconceivable to think that we can simplify this technique over the coming decade and make it robust enough to be used in a conventional clinical setting," he said. —*Linda Roach*

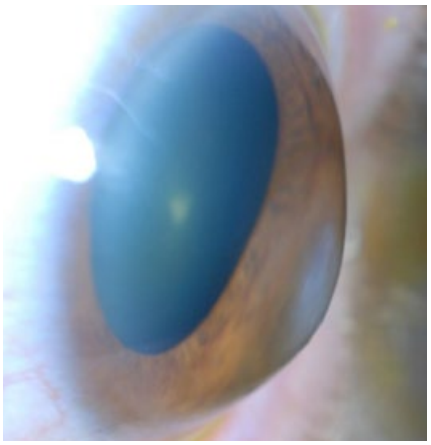
1 Jung H et al. *Commun Biol.* 2018;1:189.
2 Jung H et al. *JCI Insight.* 2019;4(6):e124904.
Relevant financial disclosures — Dr. Tam: None.

CORNEA

Keratoconus Progression: Assessing Risk

A REVIEW OF STUDIES ON THE natural history of keratoconus has found that children and those with a maximum keratometry (K_{max}) steeper than 55 D at presentation have a significantly higher risk of disease progression.[1] These patients need careful monitoring and a lower threshold for collagen cross-linking (CXL) to prevent further disease progression, the authors said.

The findings emerged from a sys-



EVALUATION. *Keratoconus patients who have steeper corneas and those who are younger at presentation may need more frequent follow-up.*

tematic review of 41 publications. Of these, 23 studies with 12-month outcomes were included in a meta-analysis. "It was surprising how few modern studies have investigated the natural progression of keratoconus," said Alex C. Ferdi, MD, at the University of Sydney in New South Wales, Australia. "Yet knowledge of the natural history is crucial to understanding progression and hence the need for interventions such as CXL."

At greatest risk. The results indicate that young patients progress more aggressively than adults; those younger than 17 years were more likely to have more than 1.5 D of K_{max} progression at 12 months. With regard to the severe progression noted among all patients with steeper K_{max} at initial assessment, those with greater than 55 D K_{max} at presentation were likely to progress by at least 1.5 D K_{max} at the one-year mark.

In addition, Middle Eastern patients experienced more progression over 12 months than did European and East Asian patients, the researchers found. They called for further studies to clarify the influence of ethnicity on keratoconus progression.

A note on topography. Earlier studies demonstrated that progression was associated with significant changes in visual acuity and refraction.[2,3] In contrast, this meta-analysis found no significant progression related to changes in these factors. In addition, the rate of thinnest pachymetry change was not clinically significant. While these are important aspects of progression, they may be less sensitive measures of progression than topography, the researchers suggested.

In the clinic. Dr. Ferdi advised clinicians to consider age and corneal parameters when evaluating the risk of progression and the risks and benefits of CXL. His institute has increased the frequency of follow-up visits for patients with keratoconus who have steeper corneas and are at younger age at presentation. In addition, they now have a lower threshold for recommending CXL in such patients.

Dr. Ferdi also urged clinicians to report patient data to the Save Sight Keratoconus Registry (https://frbresearch.org). "Our study highlighted an urgent need to collect data on keratoconus to add to our knowledge of disease natural history and to understand treatment outcomes and how individual patients respond to CXL," he said. —*Miriam Karmel*

1 Ferdi AC et al. *Ophthalmology*. Published online March 8, 2019.

2 Tuft SJ et al. *Ophthalmology*. 1994;101(3):439-447.

3 Wagner H et al. *Cont Lens Anterior Eye*. 2007;30(4):223-232.

Relevant financial disclosures—Dr. Ferdi: None.

GLAUCOMA

Following CRVO, Who's at Risk of Developing NVG?

WHEN DOCTORS IN MIAMI OBSERVED high rates of neovascular glaucoma (NVG) in patients who had experienced a central retinal vein occlusion (CRVO), they set out to identify risk factors that could predict the blinding complication. Three risk factors were associated with that progression—and affected patients should be followed at closer intervals and informed of the greater risk of neovascularization, the researchers said.

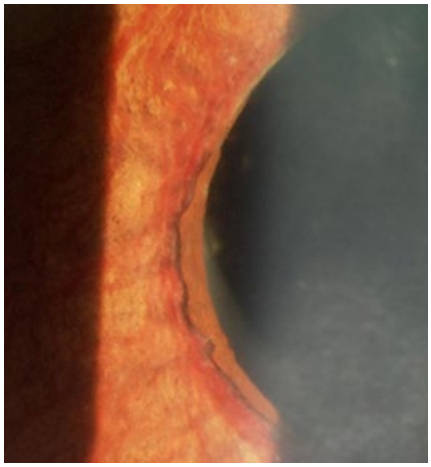
Risk of progression. In a five-year retrospective review of medical records, the researchers found that 13 of the 98 CRVO patients in their series (13%) progressed to NVG.[1] The mean adjusted time from CRVO-related symptoms to diagnosis of NVG was 212 days.

Three key risk factors emerged.

- History of systemic hypertension. This factor has not previously been reported.
- Relative afferent pupillary defect (RAPD). Patients with a RAPD had a relative risk increase of 2.15, at least doubling the probability that the eye will develop NVG. The researchers suggested that a simple pupil exam at each visit should identify the presence of RAPD and determine the course of follow-up care.
- Poorer visual acuity. For every 0.5 logMAR visual acuity worse on presentation, the risk of NVG increased 1.7 times.

No association. Age, body mass index, history of diabetes, and degree of diabetic retinopathy were not associated with NVG. In addition, history of glaucoma did not significantly differ among patients who did and did not develop NVG.

Note on macular edema. Of the 98 CRVO patients, 67 (68%) had macular edema (ME) on initial presentation. Of these, 54 were imaged with optical coherence tomography. When these 54 patients were subdivided according to their NVG status, mean central retinal thickness was 632 ± 221 µm in patients with NVG and 632 ± 335 µm in those without NVG. This corroborates



ADVANCED CASE. *Iris ectropion and prominent iris neovascularization are evident in this case of NVG.*

earlier findings that ME and NVG are independent, unrelated sequelae of CRVOs. "Thus, the clinician should not be lulled into a false sense of security after resolution of macular edema," as improved ME is not a surrogate for decreased neovascular risk, said Andrew J. Rong, MD, at Bascom Palmer Eye Institute in Miami.

Note on anti-VEGF treatment. As anti-VEGF therapy is used to treat CRVO-related ME, the researchers hypothesized that an anti-VEGF injection given on presentation could "decrease the acute ischemic burden in CRVO and provide a long-lasting protective effect against NVG development," said Dr. Rong. "Instead, we saw that anti-VEGF therapy merely delayed the onset of NVG." Despite this finding, the researchers advised injecting patients when following CRVO patients.

—Miriam Karmel

1 Rong AJ et al. *Am J Ophthalmol.* Published online March 9, 2019.

Relevant financial disclosures—Dr. Rong: None.

ONCOLOGY

Assessment of Cancer Staging System

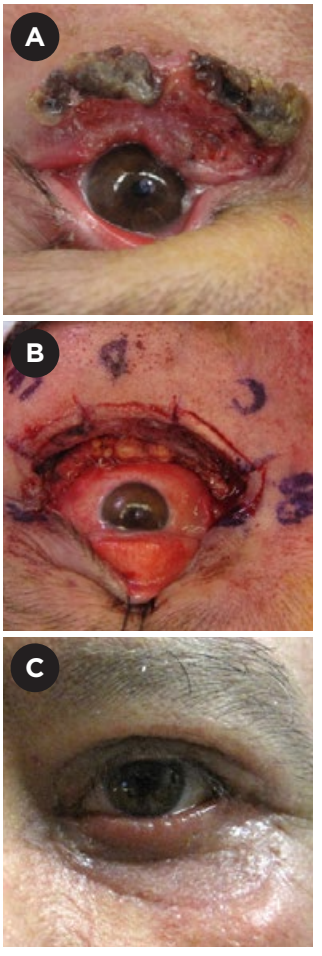
RESEARCHERS HAVE CONDUCTED a validation study of the recently published *AJCC Cancer Staging Manual,* eighth edition (*AJCC 8*) and have found significant changes in definitions of tumor (T) and lymph node (N) categories. Whereas the T category definitions in *AJCC 7* included perineural invasion and subjective terms, these criteria were removed in *AJCC 8*.

"T category distribution in *AJCC 7* differed significantly from T category distribution in *AJCC 8*," said lead investigator Bita Esmaeli, MD, at MD Anderson Cancer Center in Houston.

"In our study, we found that *AJCC 8* allows for a more precise designation of T category and a more homogeneous distribution of eyelid squamous cell carcinomas across the T categories."[1]

Comparison of classifications. In this single-center cohort study of 109 patients with eyelid and periocular squamous cell carcinoma, T category differed in 33 patients.

Twenty patients with T3 disease per *AJCC 7* had T4 disease per *AJCC 8*. Local recurrence-free survival seemed better for patients with T4 than for those with T3 tumors, and the proportion of patients with local recurrence was higher among those with T3 tumors. Similarly, six patients with histologic perineural invasion, classified as T3a disease in *AJCC 7*, had T2a or T2b disease when classified by *AJCC 8*.



SQUAMOUS CELL. *This patient's lesion was at least a T2c (A). The margins were clear on frozen section (B). The immediate reconstructive outcome after a tarsoconjunctival flap and a full-thickness skin graft (C).*

Bita Esmaeli, MD

Main outcomes and measures. Main outcomes measured in this study were local recurrence, nodal metastasis (NM), distant metastasis, and disease-specific survival (DSS).

Forty-three patients presented with recurrent eyelid or periocular squamous cell carcinoma, and 11 patients developed local recurrence during follow-up. NM was significantly associated with T category at presentation and was more common in patients with T2c, T3a, and T3b or more advanced tumors. NM at presentation and follow-up was associated with increased risk of distant metastasis. For patients with T4 disease, the two-year DSS rate was 92.6% and the five-year DSS rate was 87.7%. DSS was significantly worse in patients with T2c, T3a, and T3b or more advanced tumors. T4 disease was associated with worse DSS, but NM at presentation was not.

Limitations. This study was retrospective, and the univariate factors could be associated with one another. Due to the small number of events in each category, a multivariate analysis was not possible.

Conclusions. The bottom line: *AJCC 8* shows better predictive value in terms of local recurrence and DSS. Immunosuppression and presentation with recurrent disease are associated with increased risk of future local recurrence.

Patients with tumors of clinical stage of T2c or worse at presentation in the *AJCC 8* are at higher risk of NM and worse DSS and should undergo surveillance for NM, the authors said.

—Arthur Stone

1 Xu S et al. *JAMA Ophthalmol.* Published online March 14, 2019.

Relevant financial disclosures—Dr. Esmaeli: None.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Immediate Versus Delayed Spectacle Use in Toddlers With Moderate Hyperopia

June 2019

Although there is consensus that eyeglasses should be prescribed for children with moderate hyperopia and strabismus or amblyopia, optimal management of moderate hyperopia in the absence of the other conditions is unclear. **Kulp et al.** compared two strategies for young children with moderate hyperopia but no manifest strabismus: immediate use of eyeglasses versus observation only (unless circumstances warranted otherwise). Their findings were inconclusive but suggest that immediate spectacle use may confer a small or moderate benefit in some cases.

This randomized study included 130 toddlers (1- and 2-year-olds) with hyperopia ranging from +3.00 D to +6.00 D spherical equivalent (SE) in at least one eye, anisometropia ≤1.50 D SE, astigmatism ≤1.50 D based on cycloplegic refraction, and no evident strabismus. Patients were assigned randomly to receive eyeglasses (1.00 D less than the full cycloplegic hyperopia) or observation. Follow-up visits occurred every six months for three years.

During follow-up, children in the observation group were prescribed eyeglasses if they met prespecified deterioration criteria for distance visual acuity (VA) for age norm, if near stereoacuity fell below age norm, or if strabismus became evident. These criteria also were used to define failure in both study arms at the three-year mark.

All told, 106 children (82%) completed all three years of follow-up. There was no significant difference in failure rate between the two groups. Failure occurred in 21% of the spectacle group (11 of 53) and in 34% of the observation group (18 of 53; p = .14). In addition, 62% of the observation group and 34% of the spectacle group met the criteria for VA deterioration (e.g., requiring eyeglasses if not wearing them).

This study was limited by unsatisfactory enrollment, and the investigators acknowledged that larger studies are warranted to better estimate the effects of spectacle treatment in this age group and to determine the best approach for managing moderate hyperopia. However, it is clear from this study that whether or not spectacles are prescribed, VA deterioration is not uncommon, and young children with hyperopia should be monitored closely by eye care professionals.

The iStent inject for POAG: Safety and Efficacy Results

June 2019

Microinvasive glaucoma surgery (MIGS) may offer sustained reduction of intraocular pressure (IOP) while avoiding the drawbacks of ocular hypotensive drugs and filtering surgery. The first FDA-approved MIGS device, the iStent (Glaukos), has been used successfully in patients with open-angle glaucoma undergoing concomitant cataract surgery. A newer device, the iStent inject Trabecular Micro-Bypass System (also by Glaukos), creates two patent bypasses through the trabecular meshwork. **Samuelson et al.** looked at the safety and effectiveness of combining this approach with cataract surgery in patients with mild or moderate primary open-angle glaucoma (POAG). Relative to cataract surgery alone, the system achieved greater IOP reductions, and the two-year safety profile was good.

This multicenter study included 505 eyes with mild or moderate POAG that also required cataract surgery. Preoperative IOP was ≤24 mm Hg (with one to three medications), and unmedicated diurnal IOP ranged from 21 mm Hg to 36 mm Hg. After uncomplicated cataract surgery, eyes were randomized intraoperatively to receive either the iStent inject (treatment group, n = 387) or no stent (control group, n = 118). Follow-up lasted two years and included annual washout of ocular hypotensive medication. The effectiveness endpoints were ≥20% reduction from baseline to month 24 in unmedicated

diurnal IOP and change in unmedicated diurnal IOP from baseline to month 24. Safety measures included gonioscopy, pachymetry, and slit-lamp and fundus examinations; visual field and acuity tests; and documentation of adverse events.

The preoperative mean medicated IOP was 17.5 mm Hg in both groups; mean unmedicated diurnal IOP was 24.8 ± 3.3 mm Hg in the treatment group and 24.5 ± 3.1 mm Hg in controls. By 24 months, 75.8% of treated eyes and 61.9% of control eyes had a reduction from baseline in unmedicated diurnal IOP of at least 20% ($p = .005$). The mean reduction was greater in the treatment group (7.0 vs. 5.4 mm Hg; $p < .001$).

Among responders, 84% of treated eyes and 67% of control eyes were not receiving ocular hypotensive agents at 23 months. By month 24, medication-free diurnal IOP ≤18 mm Hg was achieved in 63.2% of treated eyes and 50.0% of control eyes. The safety profiles were favorable and similar.

Is Subthreshold Nanosecond Laser Safe for AMD?

June 2019

In preclinical studies and a pilot study, the subthreshold nanosecond laser (SNL) suggested promise in patients with intermediate AMD (iAMD). Building on these findings, **Guymer et al.** performed a randomized trial of the efficacy and safety of SNL as treatment for iAMD. For patients without signs of late AMD on multimodal imaging (MMI), the authors observed similar progression rates for the SNL and sham groups.

This 36-month, multicenter, double-masked study included 292 patients with bilateral large drusen and no sign of atrophy as seen on optical coherence tomography. Participants were assigned randomly to receive either Retinal Rejuvenation Therapy SNL (2RT, Ellex; n = 147) or a sham procedure (n = 145) in the study eye. Each treatment was given at six-month intervals. The primary efficacy outcome was the time until occurrence of late AMD, defined by MMI.

As the speckled-beam profile of the 2RT laser causes selective RPE loss, it is biologically plausible that the laser's effect may vary according to the degree of RPE dysfunction. To investigate this, the authors conducted a post hoc comparison of data for patients with and without reticular pseudodrusen (RPD) or pigmentary abnormalities at baseline. Adverse events were documented to assess safety.

Overall, the SNL treatment showed no significant benefit for slowing AMD progression (adjusted hazard ratio [HR], 0.61; $p = .122$ vs. sham). However, the post hoc analysis found evidence of effect modification based on the coexistence of RPD (adjusted interaction; $p = .002$). SNL treatment resulted in slower progression in the 222 participants without RPD at baseline (adjusted HR, 0.23; $p = .002$) and faster but nonsignificant progression in the 70 patients with RPD (adjusted HR, 2.56; $p = .112$). There were no significant differences in serious adverse events between the study groups. Although no serious events were related to the device, deep retinal hemorrhage occurred in 10 patients (6.8%) at the site of laser delivery.

The efficacy results suggest that SNL treatment may help to slow AMD progression in the absence of RPD, but it could hasten the AMD process in patients with coexisting RPD. Therefore, the authors recommended caution when considering studies of SNL use in patients with RPD phenotypes. Based on evidence from this study, further trials of the 2RT laser in AMD are warranted, they said. *(Also see related commentary by Philip J. Rosenfeld, MD, in the same issue.)*

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MPH

Can OCT Be Used to Evaluate Advanced Glaucoma?

May/June 2019

The common assumption is that optical coherence tomography (OCT) cannot be used to monitor eyes with advanced glaucoma. **Lee et al.** set out to examine the validity of this assumption by exploring the hypothesis that if eyes with advanced glaucoma have a 10-2 total deviation map with any points better than –8 dB, then the topographically corresponding regions on the circumpapillary retinal nerve fiber layer (cpRNFL) should show a preserved region. They found evidence to support this hypothesis and concluded that OCT scanning can be used to follow these preserved regions.

For this retrospective study, the researchers examined the cpRNFL scans of 39 eyes (33 patients). All eyes had a 24-2 visual field (VF) with a mean deviation (MD) of –15 dB or worse (mean, –18.94 ± 2.95 dB; range, –27.06 to –15.01 dB). 10-2 VFs and averaged OCT circle scans were available for all eyes. (The circle scans were acquired in a high-speed mode and set to average 100 times.)

When the circle scans were inspected, all 39 eyes showed a recognizable cpRNFL in the region associated with the macula. In 36 of the eyes, the cpRNFL region was clear and hyperdense. The other three eyes demonstrated visible cpRNFL, but it was of low contrast.

The authors cautioned that this study has several limitations, including a small sample size and the study's retrospective nature. In addition, they said, the assessment of cpRNFL was qualitative. As a result, they called for a prospective study of eyes that have advanced glaucoma defined by a 24-2 VF MD worse than –15 dB, quantitative cpRNFL measurements, or both.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

International Practice Patterns in Postsurgical Endophthalmitis

June 2019

Solima et al. set out to study current practice patterns for the management of eyes with acute endophthalmitis following cataract surgery and intravitreal injections. They also assessed the likelihood that an affected eye would be

managed with pars plana vitrectomy (PPV) or intravitreal injections of antibiotics. They found that PPV was frequently performed in these eyes, regardless of the presenting vision—and that eyes with increased vitreous opacification were commonly managed with PPV.

For this retrospective nonrandomized study, the researchers evaluated data on 237 eyes with acute endophthalmitis. The information was provided by 57 retina specialists in 28 countries in Africa, Asia, Europe, and South America. Outcome measures included rates of PPV, repeat intravitreal injections, and adjunctive therapeutic regimens.

Of the 237 eyes diagnosed with acute endophthalmitis, 153 (64.6%) had undergone cataract surgery, 35 (14.8%) had received intravitreal injections, and 29 (12.2%) were diagnosed following a previous PPV. The remaining 20 eyes (8.4%) had undergone other intraocular surgeries, including glaucoma and cornea procedures.

With regard to treatment, all eyes received intravitreal antibiotics on the day of presentation. PPV was performed within the first week of presentation in 176 eyes (74.3%), while the remaining 61 eyes (25.7%) received antibiotics only. Data were available on the choice of antibiotic for 210 of the 237 eyes—of these, 191 received a combination of two drugs, most commonly vancomycin and ceftazidime (183 eyes). Early PPV was more likely in those eyes that developed endophthalmitis following cataract surgery and in those in which the disc and macula were not visualized. In addition, PPV was not limited to eyes with baseline light perception vision.

The authors emphasized that these results need to be interpreted with caution, given the study's uncontrolled retrospective design and absence of data from U.S. retina practices, among other factors. *(Also see related commentary by Bernard H. Doft, MD, in the same issue.)* —*Summary by Jean Shaw*

NOW IN PUBMED

Ophthalmology Retina is now being indexed in PubMed. The indexing process is underway with this year's issues; a request has been submitted for retroactive indexing to the inaugural issue (January/February 2017).

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Update on Rubella-Associated Uveitis

June 2019

Although vaccination programs have nearly eliminated congenital rubella virus from the Western world, associations of rubella with Fuchs uveitis syndrome (FUS) were noted in 2006. Since then, many have assumed that these conditions are linked. To explore this possibility, **Groen-Hakan et al.** evaluated clinical and lab findings of patients with rubella virus–positive uveitis, as well as aqueous humor samples from patients with FUS. The authors found that even though most cases of FUS included intraocular rubella infection, only some patients with rubella-associated uveitis displayed FUS.

This retrospective study, conducted between January 2010 and October 2016 at two sites in the Netherlands, involved consecutive patients with rubella virus–positive aqueous humor samples based on polymerase chain reaction (PCR) and/or Goldmann-Witmer coefficient (GWC) analysis. Anatomic classification and clinical characteristics were recorded, along with vaccination status. All patients with FUS received their diagnosis during the same period.

Among the 127 study participants (144 eyes), the virus was found in the aqueous fluid of 120 patients by GWC, 23 by PCR, and in 16 by both. Bilateral involvement was present in 17 patients (13%). Of the 39 patients with FUS phenotype, evaluated separately, 37 had positive rubella findings.

Blurred vision and floaters were common reasons for referral; ophthalmologic evidence included the combination of chronic anterior uveitis, keratic precipitates, vitritis, and absent posterior synechiae. Early development of cataracts and glaucoma was common, and cataract was the main cause of visual loss at presentation. Cystoid macular edema was unusual. None of the patients had been vaccinated against rubella virus at an early age.

This research not only negates the belief that rubella-associated uveitis always presents with the FUS phenotype but also exposes the diverse clinical nature of the condition, which often includes chronic unilateral anterior uveitis and vitritis. The authors stressed the importance of long-term IOP monitoring in patients with rubella-associated uveitis and emphasized diagnostic accuracy to ensure that immunosuppressant therapy is reserved for those who need it.

Cataract Surgery and Visual Field Progression in POAG

May 2019

Comorbid cataract and glaucoma present a clinical challenge, as glaucoma treatment can hasten cataract development, and the presence of cataract causes diffuse visual field (VF) loss. **Kim et al.** hypothesized that cataract surgery would slow rates of VF decay in patients with primary open-angle glaucoma (POAG), compared with rates during cataract progression. However, they found that despite improvement in intraocular pressure (IOP), VF decay accelerated significantly.

The authors reviewed medical records of patients with POAG who had four or more reliable VFs before and after cataract surgery, which involved placement of an IOL. The operations occurred during a 12-year period. The researchers also looked at a comparison group of pseudophakic eyes that had 10 reliable VFs after surgery. They then used the Glaucoma Rate Index (GRI), a new algorithm, to estimate the rate of change for the entire VF.

Among the 134 study eyes (99 patients; mean age, 66 years), the mean follow-up periods were 6.5 years before and 5.3 years after surgery. All IOP parameters improved after surgery. However, except for patients with previous trabeculectomy, VF indexes (mean ± standard deviation per year) showed

worsening rates of decay after cataract surgery versus beforehand.

Higher postoperative peak IOP and worse baseline mean deviation (MD) correlated significantly with faster postoperative peak VF decay. Subgroup analysis showed that VF decay measured by MD, VF index, and GRI was worse in the latter half of the postoperative period, which may relate to the nonlinear natural history of glaucoma.

In addition to concluding that reduced IOP after cataract surgery does not slow VF decay in POAG, the authors suggested that high postoperative peaks in IOP may signal further decline after surgery.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

High Calcium Intake May Slow Progression of AMD

May 2019

Studies of the effect of calcium intake on age-related macular degeneration (AMD) have produced conflicting results. In a secondary analysis of patients in the Age-Related Eye Disease Study (AREDS), **Tisdale et al.** evaluated the relationship between baseline calcium intake and the progression of AMD. They found that higher levels of dietary and supplementary calcium were linked to lower likelihood of progression to late AMD.

Baseline self-reported intake of dietary and supplementary calcium was documented during AREDS, then analyzed in relation to outcomes. The main outcome was the occurrence of late AMD, geographic atrophy (GA), or neovascular AMD. The 4,751 participants were predominately white (96%) and female (56%); their mean age was 69.4 years.

Compared with patients in the lowest quintile for dietary calcium intake, those in the highest quintile had a lower risk of late AMD (hazard ratio [HR], 0.73), central GA (HR, 0.64), and any GA (HR, 0.80). The risk of neovascular AMD was lower for patients in the highest tertile for calcium supplementation (HR, 0.70) than for those who did not take supplements. No adverse effects were noted.

Although the findings indicate that dietary and supplemental calcium may aid in protecting against late AMD, the authors acknowledged that chance, uncontrolled confounding, and recall bias might have contributed to the results, and they noted that increased calcium intake could simply reflect better overall health habits. They encouraged further investigation of the topic. *(Also see related commentary by Mårten E. Brelén, BMBCh, FRCOphth, PhD, Danny S. Ng, FRCS, MPH, and Carol Y. Cheung, PhD, in the same issue.)*

Effect of Impaired Visual Development on Self-Perception of Young Children

May 2019

Birch et al. looked at the relationship between amblyopia and self-perception in young children to assess whether altered self-perception correlates with impaired vision or fine motor skills. They found that children with amblyopia believed that they had lower peer acceptance and physical competence. Self-perception of physical competence among children with amblyopia correlated with aiming/catching skills and stereoacuity in their study.

This cross-sectional study was conducted at a pediatric vision lab from January 2016 to May 2018. The researchers enrolled 110 healthy children between the ages of 3 and 7. Sixty of the children had amblyopia; 30 did not have amblyopia but had been treated for strabismus, anisometropia, or both; and 20 served as age-matched controls. Self-perception was assessed using the Pictorial Scale of Perceived Competence and Social Acceptance for Young Children, which includes the domains of cognitive competence, peer acceptance, physical competence, and maternal acceptance. Fine motor skills were evaluated with the Manual Dexterity and Aiming and Catching scales of the Movement Assessment Battery for Children (second edition). Visual acuity and stereoacuity were assessed as well.

Compared with controls, children with amblyopia (28 girls, 32 boys; mean age, 6.3 years) had lower mean scores for self-perception of peer acceptance (2.74 vs. 3.11; p = .04) and physical competence (2.86 vs. 3.43; p = .009). Among the children with amblyopia, self-perception of physical competence correlated strongly with aiming and catching skills ($r = 0.43$; p = .001) and stereoacuity ($r = -0.39$; p = .02). The mean physical competence scores for children without amblyopia who were treated for strabismus or anisometropia were lower than the scores for controls (2.89 vs. 3.43; p = .03).

The researchers noted that fine motor skills are essential to supporting the emergence of a child's independence and are crucial for developing positive self-esteem, proficiency, and academic skills. Further research is needed to determine whether rehabilitating visual acuity or stereoacuity would enhance self-perceptions in this age group.

Algorithm to Identify Ocular Conditions From EHR Data

May 2019

For "big data" research, investigators are tasked with identifying many patients with a disease or phenotype of interest. Often this is accomplished by relying on administrative billing codes alone. **Stein et al.** set out to devise a method to identify the presence or absence of specific ocular conditions using data from electronic health records (EHR). They developed, tested, and validated an algorithm to determine the presence/absence of exfoliation syndrome (XFS). Their approach proved superior to using billing codes alone.

This retrospective analysis involved EHR data for 122,339 patients in the Sight Outcomes Research Collaborative Ophthalmology Data Repository who received eye care at participating centers from August 2012 through August 2017. The researchers developed a comprehensive algorithm that searches structured and unstructured (free text) EHR data for conditions of interest. They then tested its ability to detect the presence or absence of XFS among a sample of patients with and without

XFS (n = 200) by reviewing ICD-9/ICD-10 billing codes, the patient's problem list, and text within the ocular exam section and the unstructured (free-text) section of the EHR.

The likelihood of XFS was estimated for each patient using logistic least absolute shrinkage and selection operator regression. The EHR data of all patients were run through the algorithm to generate an XFS probability score for each patient, and the algorithm was validated through EHR review by glaucoma specialists. The positive predictive value (PPV) and negative predictive value (NPV) of the algorithm were computed as the proportion of patients classified correctly as having or not having XFS.

The algorithm assigned XFS probability of less than 10% to 99% of patients (n = 121,085), probability of greater than 75% to 0.4% (n = 543), probability of greater than 90% to 0.3% (n = 353), and probability of greater than 99% to 0.07% (n = 83). According to the analysis by glaucoma specialists, the algorithm's PPV was 95% and NPV was 100%. When there was an ICD-9 or ICD-10 billing code for XFS, there also was XFS evidence elsewhere in the EHR in 86% or 96% of records, respectively. However, with clinical or free-text evidence of XFS, coexistence of ICD-9 codes was less common (~40%), and ICD-10 codes were even more scant (~20%). *(Also see related commentary by Kurt K. Benke, PhD, in the same issue.)* —*Summaries by Lynda Seminara*

OTHER JOURNALS

Selected by Deepak P. Edward, MD

PDL Treatment of Port-Wine Stains Without General Anesthesia in Infancy

JAMA Dermatology
Published online March 13, 2019

Recent concerns about repetitive use of general anesthesia in young children and infants have rekindled the debate on when to start laser treatment for port-wine stains. **Jeon et al.** reviewed outcomes for patients who began pulsed dye laser (PDL) therapy, without anesthesia, in the first year of life. They found the treatment to be effective as well as safe, with more than two-thirds of the treated children experiencing outcomes that were excellent or better.

For this study, the authors reviewed medical records of 197 children who received PDL therapy for port-wine stains at ≤1 year of age; treatment occurred between 2000 and 2017. The mean age at initial treatment was 3.38 months (range, 5-355 days), and the mean number of treatments per patient was 9.8 (range, 2-23). Most of the children (n = 149; 76%) had port-wine stains on their faces. Metal corneal shields were used to protect children who had lesions that involved the periocular region.

The primary outcome was improvement of the vascular birthmarks. Before-and-after images were graded by four physicians according to a five-point visual analog scale (VAS), with 1 = poor (0%-25% improvement) and 5 = complete (100% clearance). All told, 51 of the children (25.9%) had complete clearance, 81 (41.1%) had an excellent outcome, 44 (22.3%) had good results, 13 (6.6%) had fair outcomes, and eight (4.1%) had poor results. The mean VAS score was 3.65 (standard deviation, 1.26), denoting excellent clearance. The presence of a lesion at V1 (the first branch of the trigeminal nerve) correlated significantly with a higher clearance rate. No patient had scarring or a permanent change in pigment.

Based on the results, the authors support early in-office treatment of infants with port-wine stains, particularly if the patient's risk for complications is minimal. Early intervention with PDL therapy allows for treatment without general anesthesia, maximizing the likelihood of clearance before school age and, in turn, minimizing the negative consequences of these birthmarks.

DR and Diabetic Kidney Disease Are Risk Factors for Mortality

JAMA Network Open
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Sabanayagam et al. assessed the relationship between diabetic retinopathy (DR), diabetic kidney disease (DKD), and mortality in a large Asian population. They found that the presence of either condition is linked to higher risk of all-cause and cardiovascular-related mortality and that the risk is greater with DKD.

For this study, the researchers evaluated 2,964 adults with diabetes who participated in the Singapore Epidemiology of Eye Diseases study. Participants ranged from 40 to 80 years of age (mean, 61.8 years) and were Chinese (n = 592), Malay (n = 1,052), or Indian (n = 1,320). DR was identified from retinal photographs, and DKD was established from estimated glomerular filtration rates; these analyses revealed that 30% of the study population had DR, and 21% had DKD. Data for all-cause and cardiovascular disease (CVD) mortality were gathered from the National Registry of Births and Deaths.

During the median follow-up period of 8.8 years (range, 7.2-11.0 years), 610 deaths occurred (20.6% of the study population). Of these, 267 deaths were attributed to CVD. In separate models for all-cause and CVD mortality, multivariable hazard ratios were 1.54 and 1.74, respectively, for DR; and 2.04 and 2.29, respectively, for DKD. In models that included both DR and DKD, the subgroup with DKD alone contributed strongly to the excess risk of all-cause and CVD mortality (27.1% and 12.6%, respectively), followed by the subgroup with DR alone (6.5% and 5.2%). Compared with patients who had neither DR nor DKD, the hazard ratios for all-cause and CVD mortality were 1.89 and 2.26, respectively, for DKD alone and 1.38 and 1.64, respectively, for DR alone. For patients with DR as well as DKD, the respective hazard ratios were 2.76 and 3.41. The relative excess risk of the DR/DKD interaction was 0.49 (p = .20) for all-cause mortality and 0.51 (p = .50) for CVD mortality.

The authors concluded that the risk of all-cause and CVD mortality is high for patients with DKD and/or DR, and that DKD confers a greater risk than DR. Their findings highlight the importance of early identification, close monitoring, and proper management of these conditions to reduce the risk of death, particularly in Asian populations. —*Summaries by Lynda Seminara*

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When Aqueous Is Misdirected During or After Cataract Surgery

Aqueous misdirection related to ocular surgery is, most often, a postoperative phenomenon. Although intraoperative instances are considered rare, most busy cataract surgeons will experience this phenomenon a few times during their career, said Marjan Farid, MD, at the University of California in Irvine. When it does manifest during surgery, it can be confused with another alarming condition: suprachoroidal hemorrhage. "We don't see aqueous misdirection very often, so it can take us by surprise. You have to keep it in the back of your mind, be vigilant, and do what you can to prevent or treat it," said Lucy Q. Shen, MD, at Massachusetts Eye and Ear in Boston.

Armed with an understanding of the condition and awareness of risk factors, the surgeon can take steps pre-, intra-, and postoperatively to manage this potentially vision-threatening entity.

What Is Aqueous Misdirection?

Traditionally, the term aqueous misdirection describes a postoperative condition in which aqueous humor accumulates in the vitreous cavity, causing high IOP and uniform shallowing of the anterior chamber. It is also called malignant glaucoma.[1]

Irrigation misdirection. Similarly, intraoperative disruption of fluidic homeostasis can cause fluid from the anterior chamber to misdirect posteriorly, resulting in a shallow anterior chamber and elevated IOP. After ruling out a suprachoroidal hemorrhage, one can only assume that this is caused by infusion or irrigation misdirection, said Nicole R. Fram, MD, who practices in Los Angeles. This occurrence has also been referred to in the literature as acute intraoperative rock-hard eye syndrome.[2] But some surgeons consider it a type of aqueous misdirection, said Dr. Shen.

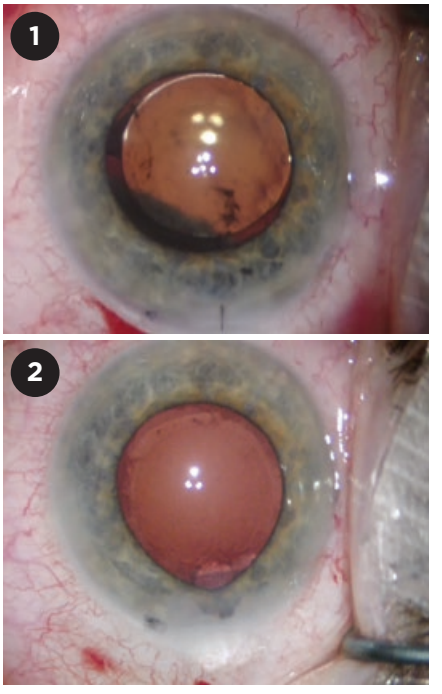
Who Is at Risk?

Eyes at greater risk both intraoperatively and postoperatively include those with shorter axial length or angle closure, where the outflow pathway is narrow or already compromised, said Dr. Farid.

"Problems with the zonular apparatus may cause aqueous to travel back through the zonules and get trapped in the vitreous cavity," said Dr. Farid. Eyes with compromised zonules tend to be those with pseudoexfoliation or uveitis, as well as those that have undergone laser iridotomy, vitrectomy, trabeculectomy, or insertion of a glaucoma drainage device, said Dr. Fram.

Notably, aqueous misdirection during a previous surgery confers increased risk for the fellow eye.[1]

The exact underlying mechanism of aqueous misdirection is unclear, but it is thought to involve an abnormal relationship between the ciliary processes, lens, anterior vitreous, and possibly choroid, causing aqueous to divert into the vitreous cavity.[1]



WHICH IS WHICH? *(1) The shadow in the red reflex indicates a suprachoroidal hemorrhage. (2) Iris prolapse and anterior chamber shallowing, indicating aqueous misdirection.*

Preventive Steps

Careful planning for anterior segment surgery includes the following steps, said Dr. Shen.

Position the head. Before the patient is draped for surgery, make sure the head is positioned above the body. This can be done by inclining the torso slightly so that the patient is resting in a

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **MARJAN FARID, MD, NICOLE R. FRAM, MD,** AND **LUCY Q. SHEN, MD**.

Nicole R. Fram, MD

very elongated Z-shape. This positioning can decrease the risk of posterior pressure from the weight of the body, which is particularly important if the patient has a large body habitus, said Dr. Shen.

Elevate the speculum. Another way to lessen posterior pressure is to elevate the lid speculum a little, said Dr. Shen. "Put a couple of 4 × 4 gauzes underneath the speculum to reduce the pressure to the orbit and, consequently, the pressure on the globe."

Minimize manipulation. When doing cataract surgery, the surgeon should minimize manipulation and get in and out as quickly as possible, said Dr. Farid. Also, creating a longer tunnel for the corneal incision helps to prevent iris prolapse and provides a tighter seal to help manage the situation, she said.

Inject viscoelastic. Dr. Farid recommends using a heavy cohesive viscoelastic in the anterior chamber to keep it formed throughout the case. In patients at risk for aqueous misdirection or suprachoroidal hemorrhage, Dr. Fram injects viscoelastic or balanced salt solution (BSS) every time she comes out of the eye to maintain a constant eye pressure and avoid abrupt IOP fluctuations.

Minimize manipulation and get in and out as quickly as possible.
—Dr. Farid

Dr. Shen performs the same maneuver. "The idea is to prevent the posterior lens capsule from ever touching the cornea during the case," she said.

Be gentle with inflation. If you inject BSS too forcefully, said Dr. Shen, it can be directed toward the vitreous and can result in irrigation misdirection. "Be gentle and watch the anterior chamber when inflating, so you don't push too much fluid into the posterior part of the eye."

Be watchful. Following phacoemulsification, Dr. Shen sometimes performs endoscopic cyclophotocoagulation to reduce IOP in patients with angle-closure glaucoma. "Even with this step, the patient is still at risk for intraoperative aqueous misdirection," she said. Again, ensure that you have adequate viscoelastic to maintain anterior chamber depth, she said.

Considerations for fellow-eye surgery. In one case of fellow-eye surgery, Dr. Fram chose not to perform femtosecond laser because she wanted to avoid IOP fluctuation from suction and release. "And I did surgery under general anesthesia with paralysis to avoid any possibility of posterior pressure," she said.

Dr. Shen advises considering the use of atropine at the beginning of the case and lining up a retina team in case a vitrectomy is needed.

Intraoperative Strategies

It is important to recognize aqueous misdirection when it occurs during cataract surgery, to rule out suprachoroidal hemorrhage as the cause of positive posterior pressure and hardening of the globe, and to have a directed plan of action for its management, said Dr. Farid.

Watch for signs. "When strange things start happening during surgery—the iris keeps prolapsing, wound is leaking, eye pressure is going up, and anterior chamber is shallowing—you may not believe it at first," said Dr. Farid. "Then it finally clicks in: This is aqueous misdirection." In addition to these signs, the sclera feels very hard, added Dr. Shen, hence the term, acute intraoperative rock-hard eye syndrome.

Rule out other problems. Both a retrobulbar block—which increases the volume behind the globe and produces posterior pressure behind the eye—and a choroidal hemorrhage can mimic aqueous misdirection.

Suprachoroidal hemorrhage. To help confirm the diagnosis, look for a good red reflex, said Dr. Farid. If there is a darker reflex or a shadow on the red reflex (Fig. 1), that is indicative of a hemorrhage. The presence of pain also suggests hemorrhage. Those at higher risk for hemorrhage are patients who are older, have systemic hypertension, or are taking anticoagulation drugs or undergoing large-incision surgery, said Dr. Fram.

IFIS. Also, don't confuse aqueous misdirection with intraoperative floppy iris syndrome (IFIS), in which only the iris comes out of the wound, said Dr. Shen. "The entire lens-iris diaphragm is pushed anteriorly in aqueous misdirection."

The first question to ask yourself when the iris is prolapsing is whether the eye is soft or hard, said Dr. Fram. "If the eye is soft, it might be IFIS or poor wound construction," she said. "If the eye is hard, it might also be IFIS; however, the bulging posterior capsule and movement of the entire lens-diaphragm complex should alert the surgeon to irrigation misdirection."

Wait and come back. The surgeon can stop and use an indirect ophthalmoscope to evaluate whether a suprachoroidal hemorrhage is present and can assess the patient for pain, added Dr. Fram. If you suspect, or can't confirm the absence of, a hemorrhage or large choroidal effusion—especially when the patient has no risk factors for zonulopathy or pseudoexfoliation syndrome—close the eye and come back, preferably after one week, she said, adding, "If it is a suprachoroidal hemorrhage and the surgeon places the trocar in the suprachoroidal space, the consequences can be devastating."

Keep the patient comfortable—and pause. If you suspect aqueous misdirection, first make sure the patient is comfortable, said Dr. Shen. To help prevent any tensing or squeezing, use sedation if needed, and double-check that the speculum is not applying pressure. "At this point, I would ask the nurse to give atropine—if atropine was not given at the beginning of the case," she said. "Just by waiting a bit, sometimes misdirection caused by irrigation will reverse itself."

Equilibrate the chambers. A variety of maneuvers may help equalize pressure in the eye.

Use an air bubble. If you are using a very heavy viscoelastic to re-form the anterior chamber, said Dr. Farid, you can put an air bubble in the anterior chamber to push things back. "Then, stop for five to 10 minutes to allow decompression to occur before finishing the case."

Drain fluid. You can use a needle to drain BSS that has traveled behind

the capsule, said Dr. Shen. "To avoid touching the posterior capsule, measure 3.5 mm behind the limbus and visualize the needle as you enter behind the capsule." She recommends starting with a 30-gauge needle and 1 cc syringe but suggests taking the plunger out so the pressure will equilibrate.

"The vitreous is not causing the problem intraoperatively, so technically you don't need a vitrectomy with a large-bore needle," said Dr. Shen. "All you need is to remove some of the misdirected fluid."

Do a vitrectomy. Both Dr. Fram and Dr. Farid, however, would consider a pars plana vitrectomy after ruling out a suprachoroidal hemorrhage. "Aim toward the optic nerve with the trocar about 3.5 mm posterior to the limbus," said Dr. Fram. In rare cases, where the anterior chamber is completely shallow, said Dr. Farid, you may make a small sclerotomy about 3 mm posterior to the limbus and use a small-gauge vitrector to perform a one- to two-second core vitrectomy. This will break the anterior hyaloid face and immediately release the trapped fluid.

Give mannitol. If the IOP is still over 30 mm Hg despite maneuvers, you can give mannitol at 1 g/kg, said Dr. Fram. "However, if IOP is normal, we want to avoid abrupt changes in pressure, which can cause more shearing of the choroidal vessels in the setting of suprachoroidal hemorrhage." It's important to be aware that mannitol can cause systemic complications, such as congestive heart failure or intracranial hemorrhage in at-risk patients, she said.

Postoperative Management

The likelihood of encountering aqueous misdirection increases after anterior segment surgery in at-risk patients.

Confirm the diagnosis. Confirmation of postoperative aqueous misdirection will show that the anterior chamber is shallow, the pressure is usually very high, and the lens is pushed up against the cornea, whether the patient is phakic or pseudophakic, said Dr. Shen. Dilated fundus exam or B-scan, if the view is hazy, can help rule out a choroidal effusion or hemorrhage, she added.

Although severe eye pain is uncommon postoperatively, patients may experience discomfort, redness, and decreased vision, said Dr. Fram, but aqueous misdirection is mainly a clinical diagnosis at the slit lamp. You can instill a cycloplegic eyedrop, such as atropine, in the patient's eye to move the ciliary body back and measure anterior chamber depth and configuration with anterior segment optical coherence tomography. Ultrasound biomicroscopy can also help you look for anteriorization of the ciliary body, said Dr. Fram.

Wait and watch. If the pressure is not too high, you may be able to put an air bubble into the anterior chamber at the slit lamp and wait to see if the problem resolves, said Dr. Farid. Waiting too long is obviously not an option. If the condition persists, high IOP can damage the optic nerve, and contact between the cornea and lens or IOL may damage endothelial cells, she said.

Manage with medicine. Cycloplegics such as atropine and cyclopentolate can shift the lens-iris diaphragm posteriorly, said Dr. Shen. "Aqueous suppressants such as timolol and dorzolamide can decrease the amount of aqueous produced and lower the IOP. Also, steroid medication is helpful because aqueous misdirection is often associated with inflammation and swelling of the choroid. Frequent use of prednisolone acetate every one to two hours or use of a stronger steroid such as difluprednate can help to alleviate any inflammation and associated discomfort."

Perform surgery. "The first step before undertaking a surgical procedure to relieve the pressure is to make sure there is no IOL-corneal touch," said Dr. Fram. Then, she said, "You can perform an anterior chamber paracentesis and inject a cohesive viscoelastic to temporarily push the IOL complex posteriorly and away from the cornea."

You can make an opening and communication between the iris and the vitreous through the peripheral capsule with an Nd:YAG laser, said Dr. Fram. "Or you can create this opening using a vitrector intraoperatively." Whether you do the procedure in an office or in the OR depends upon the extent of the problem and the clarity of your view, she said.

1 Moinul P, Hutnik C. *Clin Ophthalmol.* 2015;9:183-186.

2 Lau OC et al. *J Cataract Refract Surg.* 2014;40(5):799-804.

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EXTRA **MORE ONLINE.** Read about trickier cases and view the video "Aqueous Misdirection With Low Intraocular Pressure" posted with this article at aao.org/eyenet. Or watch the video with the QR code.

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Single-Pass Four-Throw Pupilloplasty: A Treatment for Angle-Closure Glaucoma?

Angle closure compounded by peripheral anterior synechiae (PAS) is one of the biggest challenges we face as glaucoma surgeons, said Sanjay Asrani, MD. PAS can irreversibly impair flow through the trabecular meshwork,[1] resulting in angle-closure glaucoma that persists despite first-line treatment. If PAS have been present for longer than six months, the chances of reestablishing function of the trabecular meshwork are very low, even if you remove the adhesions and anatomically restore the angle, said Dr. Asrani, who is at Duke University in Durham, North Carolina.

After treatment, recurrence of adhesions is a constant concern, said Alan Crandall, MD. In chronic angle-closure glaucoma, the iris often is atrophic, and conventional measures to resolve PAS deteriorate during long-term follow-up, he said. Dr. Crandall is at the Moran Eye Center in Salt Lake City.

A New Approach

In 2017, Amar Agarwal, MD, tried something different to treat angle-closure glaucoma in phakic patients. He performed a new technique—single-pass four-throw pupilloplasty (SFT)—in combination with lens extraction.[2] He found that the procedure opened the angle, released associated PAS, and secured the iris centrally to help prevent recurrence of the PAS. Dr. Agarwal is with Dr. Agarwal's Eye Hospital and Eye Research Centre in India.

Other techniques, such as a Siepser slipknot, can also be used for pupilloplasty. However, "In the evolution of anything we do surgically, we're trying to make procedures as elegant, as safe, and as cost-effective as we can," said Dr. Crandall. "And this is the case with SFT because you're placing one suture multiple times. It's much less time-consuming than a Siepser knot and just as effective."

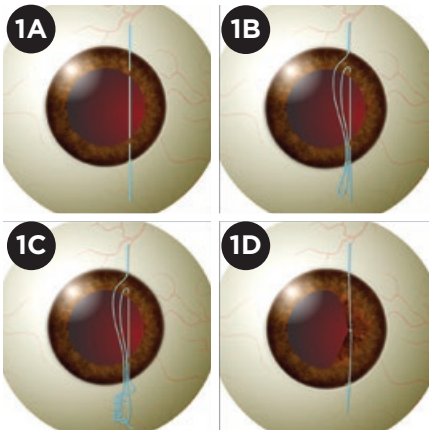
No matter what treatment is used, angle closure inevitably causes damage to the trabecular meshwork, said Dr. Asrani. But SFT and medical therapy, if implemented in the early stage of the disease, might be enough to restore aqueous flow and stabilize IOP, obviating the need for more invasive interventions such as trabeculectomy or tube surgery, he said. "When I look at this technique, I think of the patients I could have helped with it."

Traditional Treatments

First-line therapies for angle-closure glaucoma include pilocarpine eyedrops, laser surgery, goniosynechiolysis, and cataract extraction, depending on the severity and underlying cause. If initial treatment fails, surgeons usually turn to trabeculectomy or implantation of a drainage device, said Dr. Asrani.

Laser surgery. Laser peripheral iridotomy is the mainstay for pupillary-block angle closure. However, in angle closure caused by plateau iris, iridotomy will not resolve the narrow angle or prevent PAS. In these cases, argon laser peripheral iridoplasty and pilocarpine eyedrops are initial options, but over time, the iris usually migrates back to the periphery, and PAS recur, said Dr. Asrani.

Synechiolysis and lens removal. Dr. Asrani noted that even goniosynechiolysis coupled with lens removal is a temporary fix because the inflamed iris remains close to the trabecular meshwork and tends to readhere. "In contrast," Dr. Asrani said, "SFT pupilloplasty along with synechiolysis



SFT PUPILLOPLASTY. *(1A) A needle is passed through the proximal and distal portions of the iris tissue. (1B) The proximal and distal portions of the iris are approximated, and a loop of suture is withdrawn. (1C) The suture end is passed through the loop four times. (1D) When the suture ends are pulled, the loop slides inside the iris tissue, yielding a stable knot.*

Amar Agarwal, MD

BY JENNIFER S. GRIFFIN, MS, CONTRIBUTING WRITER, INTERVIEWING **AMAR AGARWAL, MD, SANJAY ASRANI, MD,** AND **ALAN CRANDALL, MD.**

prevents recurrence of PAS by keeping the pupil taut. For patients who have angle closure with a chronically dilated pupil, SFT also will improve the optics by reducing glare."

Techniques and Outcomes

Dr. Agarwal performs SFT pupilloplasty under peribulbar anesthesia, with supplemental anesthesia given as needed.[2] He prefers maintaining the anterior chamber with fluid, rather than viscoelastic, because "fluid will wash away hyphema, which may occur when PAS are broken." He also recommends using an endoilluminator for good visualization, especially if the cornea is hazy.

Technique. An end-opening forceps is used to grasp the iris and pull it toward the center of the pupil at 60-degree intervals around the pupillary margin. Dr. Crandall pointed out, "This 'pull and release' technique partially detaches the PAS and informs the surgeon about the extent of the adhesions and the amount of iris tissue available for reconstruction."

With the proximal iris held with forceps, a straight needle with a 10-0 or 9-0 nonabsorbable polypropylene suture is inserted. From the other end, a 26- or 30-gauge needle is passed through a clear-corneal incision into the distal iris. The straight needle is docked into the lumen of the 26- or 30-gauge needle, and the two are withdrawn together through the distal incision. A loop is created at the suture exit side with a Sinskey hook, and four throws of the distal end of the suture are made through this loop. The ends of the suture are pulled apart to yield a self-locking, helical knot that lies flat against the iris. The suture ends are trimmed with a microscissors, leaving 1-mm ends. (See video posted with this article at aao.org/eyenet.)

Dr. Agarwal explained his rule of thumb for SFT knot placement. "If PAS are observed around more than 270 degrees of the pupillary margin, carry out six-point traction (i.e., three SFT knots); if the PAS constitute less than 270 degrees, you only need four-point traction to sufficiently constrict the pupil."

Recent findings. In a 2018 study coauthored by Dr. Agarwal, SFT pupilloplasty was performed following cataract surgery in five patients with angle-closure glaucoma and PAS.[2] By six to eight months postoperatively, all patients had fewer PAS, an open angle, lower IOP, and better visual acuity. "As an adjunct to PAS lysis and to prevent further synechiae development, SFT makes sense theoretically, but it is early in its development," said Dr. Crandall.

Benefits of SFT

Anatomy. "In SFT pupilloplasty, you are not introducing an artificial drainage pathway, as in trabeculectomy or valve placement," said Dr. Agarwal. "Instead, you are enabling function of the existing trabecular meshwork. You are restoring, rather than changing, the anatomy." Dr. Crandall agreed, "It makes physiologic sense as treatment for chronic angle-closure glaucoma."

A simpler knot. Dr. Agarwal said that surgeons who prefer the Siepser slipknot or cerclage can adapt those pupilloplasty maneuvers to treat angle-closure glaucoma. However, Dr. Crandall noted, "SFT is technically easier, less time-consuming, and as effective as other pupilloplasty techniques."

Safety. Dr. Agarwal considers SFT to be safer than multiple-pass pupilloplasty techniques. "When you go for a second or third pass, you are manipulating the anterior chamber, and you can damage the iris and cornea," he said. Additionally, in SFT pupilloplasty, the knot is self-retaining and is not tied, thereby reducing bulk in the anterior chamber.[3]

Considerations

Despite its advantages, SFT pupilloplasty combined with lens removal is not a one-size-fits-all solution for angle-closure disease.

Phakic status. Narang et al. noted that SFT cannot be performed in phakic eyes and that lensectomy should be done in the same surgical session,[3] regardless of whether a visually significant cataract is present. However, this apparent drawback may be counterbalanced by the reported benefits of lens removal in angle-closure glaucoma. Results of a randomized controlled trial demonstrated that clear lens extraction is more efficacious and more cost-effective than laser peripheral iridotomy plus topical medical treatment in patients with primary angle closure and high IOP with or without glaucoma.[4] Nevertheless, some surgeons have questioned the validity of clear lens extraction for angle closure, given the surgical risks and loss of accommodation with lens removal.[5,6]

Inflammation. Because SFT pupilloplasty is an intraocular procedure, inflammation is a concern. "If the patient has fixed pupillary dilation with chronic angle closure in uveitis, SFT may chronically inflame the iris. Additionally, the inflamed eye structures could remain in apposition, so PAS might not be prevented," Dr. Asrani cautioned. "However, benefits of preventing PAS and reducing glare using SFT may have to be balanced with the risk of persisting iritis in such cases."

Tissue tears. "In general, the surgeon should be careful to avoid overtightening the helical knot, which could tear the iris tissue,"[3] said Dr. Agarwal. He added that extreme care should be exercised when performing SFT in eyes with secondary angle-closure glaucoma involving atrophic patches of the iris, such as in Urrets-Zavalia syndrome (UZS).[2] Nevertheless, Dr. Agarwal said that SFT pupilloplasty—performed carefully—does open the angles well in cases of UZS.

Fundus visualization. Dr. Agarwal and his colleagues reported that patients treated with SFT pupilloplasty still can undergo mydriasis, although the extent of pupillary dilation in SFT-treated eyes is less than that in untreated eyes.[7] Dr. Asrani pointed out that decreasing the pupillary opening, by means of SFT pupilloplasty, can limit the examination and treatment of retinal conditions. However, he said, "If the patient needs retinal treatment, the retinal surgeon can snip the SFT suture and reopen the pupil." Dr. Agarwal added that an Nd:YAG laser also could be used to undo the pupilloplasty.

Cosmesis. "In terms of aesthetic results," Dr. Crandall said, "pupillary cerclage is probably better than SFT. However, cerclage is technically

challenging and time-consuming. And although cerclage may appear cosmetically better, it is not functionally better, he said. Moreover, Dr. Agarwal pointed out, "Cerclage is especially difficult to perform in the setting of PAS."

Too late? "If angle-closure glaucoma goes untreated," said Dr. Agarwal, "fibrosis can occur," and SFT pupilloplasty would not be sufficient to normalize aqueous outflow. He noted, "Such patients would need additional medical treatment or even a shunt procedure or trabeculectomy."

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2 Narang P et al. *Indian J Ophthalmol.* 2018; 66(1):120-124.
3 Narang P, Agarwal A. *Eur J Ophthalmol.* 2017; 27(4):506-508.
4 Azuara-Blanco A et al. *Lancet.* 2016;388(10052): 1389-1397.
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7 Kumar DA et al. *J Cataract Refract Surg.* 2017;43(10):1307-1312.

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Dr. Asrani is professor of ophthalmology at Duke University in Durham, N.C. *Financial disclosures: Aerie: C; Bausch + Lomb: C; Camras Vision: C; Noveome Biotherapeutics: C; Regenexbio: C.*
Dr. Crandall is professor and senior vice-chair of ophthalmology and visual sciences and director of glaucoma and cataract at the Moran Eye Center, University of Utah, Salt Lake City. *Financial disclosures: Alcon: C,L; AqueSys: C; ASICO: C; Excel-Lens: C; Glaucoma Research Foundation: C; Glaukos: C; Iantech: C; iSportGames: C; Ivantis: C; iVeena: C; Johnson & Johnson: C; Mastel: C; New World Medical: C; Omeros: C.*

See the disclosure key, page 8.

EXTRA **MORE ONLINE.** Use the QR code below to view a video of the single-pass four-throw pupilloplasty technique, or find a video of the procedure posted with this article at aao.org/eyenet.

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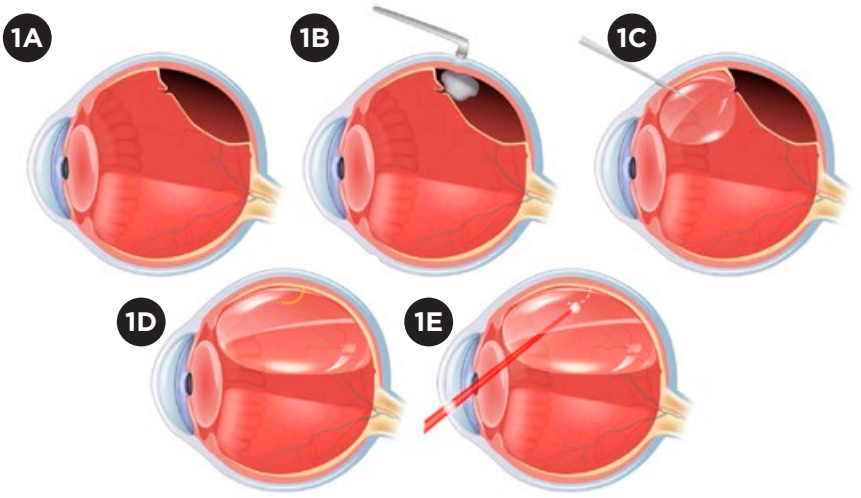
When and How to Use Pneumatic Retinopexy

First described in 1986 by Hilton and Grizzard,[1] pneumatic retinopexy (PR) is a nonincisional outpatient procedure used to treat selected cases of rhegmatogenous retinal detachment (RRD). PR is used to treat up to 15% of all retinal detachments in the United States, and it remains the most commonly employed modality for repair after pars plana vitrectomy (PPV) alone or PPV in combination with scleral buckle (SB).

PR involves the injection of an intravitreal gas or air bubble to tamponade the retinal break(s), coupled with laser retinopexy or cryoretinopexy to seal the break site(s). This two-step procedure facilitates apposition of the retina by means of the eye's innate ability to resorb subretinal fluid (Fig. 1).



STEPS IN PR. *(1A) Small retinal break allows fluid to enter the subretinal space, causing superior retinal detachment. (1B) Cryoretinopexy is used to stimulate scar formation around the edges of the break. (1C) Gas bubble is injected into the vitreous cavity. (1D) Bubble expands to cover and tamponade the retinal break. (1E) As an alternative to cryoretinopexy, laser photocoagulation can be performed around the retinal break after gas has been injected and retinal apposition is achieved.*

Indications

The ideal candidate for PR is phakic, with a single break or multiple smaller breaks spanning no more than 1 clock-hour in the superior 8 clock-hours of the fundus (Table 1, online). Relatively clear ocular media are necessary for the identification and treatment of the retinal break(s) that precipitated the RRD as well as other potential breaks in the retinal periphery.

The patient's overall physical and cognitive health, as well as social environment and lifestyle, should allow for postprocedural head positioning such that the injected gas bubble remains over the retinal break(s).

Expanded criteria. PR has also been used successfully under expanded criteria to treat large retinal breaks, as well as several smaller breaks cumulatively spanning multiple clock-hours of the retinal arc.[2,3] However, sequential alternation of head positioning may be required during the postoperative period to tamponade all retinal breaks effectively.[4] For this reason, some surgeons choose to perform primary PPV, SB, or combined SB/PPV instead of PR to improve the likelihood of single-procedure success in patients with large tears or with several smaller breaks collectively spanning more than 1 clock-hour of the superior fundus.

Contraindications

Inferior break. Although single-operation and final anatomic success in the repair of inferior RRD has been reported in the literature,[5] an inferior break is a general contraindication to PR. Even under maximal intravitreal expansion, the gas bubble may not cover the inferior retina with standard

BY **OMAR MOINUDDIN, MD, THOMAS J. WUBBEN, MD, PHD, DAVID N. ZACKS, MD, PHD,** AND **CAGRI G. BESIRLI, MD, PHD.** EDITED BY SHARON FEKRAT, MD, AND INGRID U. SCOTT, MD, MPH.

post-PR positioning. Furthermore, most patients cannot reasonably be expected to tolerate the inverted neck hyperextension or hyperflexion positioning required to tamponade an inferior break. Even in the management of an uncomplicated superior retinal break, physical or other disabilities that preclude appropriate head positioning may lead the physician to elect for SB, PPV, or both instead of PR.

Advanced glaucoma. Despite the use of anterior chamber paracentesis as part of the procedure, there is a risk for a spike in IOP with injection of gas into the vitreous cavity.[4] Thus, advanced glaucoma may be a relative contraindication to PR. In all cases, after gas injection, central retinal artery perfusion should be confirmed by means of indirect ophthalmoscopy to visualize arterial pulsations. If pulsations are absent for more than 10 minutes, repeat paracentesis should be performed immediately to lower IOP.[4]

Proliferative vitreoretinopathy (PVR). Preexisting PVR with retinal traction may result in persistent RD despite adequate PR gas tamponade of the causative break.[6] Thus, a patient with extensive PVR (grade C or D) is not a good candidate for PR.

Lens status. PR can be performed successfully in most phakic and pseudophakic patients. However, it should be avoided in patients with lens instability or aphakia because of the potential for gas bubble migration into the anterior chamber and poor tamponade of the retinal break(s).

Lattice degeneration. The presence of detachment or subretinal fluid accumulation itself is not a contraindication; surgeons may elect to perform PR if all breaks can be identified in the superior 8 clock-hours of the fundus and treated with laser or cryoretinopexy. Extensive lattice degeneration, however, may represent an increased risk for new retinal breaks and is considered a contraindication by some surgeons.[3]

Surgical Technique

Following is a step-by-step approach to PR. See also Figure 1.

1. Carefully examine the eye with indirect ophthalmoscopy and scleral depression to identify areas of pathology.

2. Anesthetize areas for cryoretinopexy treatment with subconjunctival anesthesia.

3. Perform cryoretinopexy. (Note: Alternatively, retinopexy can be performed using laser photocoagulation once retinal apposition has been achieved after gas injection.)

4. Apply povidone-iodine (Betadine) solution to sterilize the injection site.

5. Filter perfluoropropane gas (C_3F_8), sulfur hexafluoride gas (SF_6), or air into a tuberculin syringe on a 30-g needle. (See "Selection of Tamponade Agent" for considerations about these gases.)

6. Perform an anterior chamber paracentesis to remove 0.1 to 0.25 mL of aqueous humor.

7. Select a site perpendicular to the sclera, farthest away from the site of the underlying detachment, and enter 3 to 4 mm from the limbus.

8. Withdraw the needle so that only its tip remains in the vitreous cavity, then carefully inject C_3F_8 (0.2-0.3 mL), SF_6 (0.5-0.6 mL), or filtered air (0.8 mL), making sure that the needle tip is not in the suprachoroidal space.

9. Reexamine with indirect ophthalmoscopy to confirm placement of gas bubble over the retinal break(s) and perfusion of the central retinal artery (repeat paracentesis if arterial pulsations are absent).

10. Review head positioning and gas bubble precautions with the patient, with attention to later expansion of the gas bubble.

Selection of Tamponade Agent

The tamponade agent for PR is selected based on the size and duration of the bubble needed to sufficiently cover all retinal breaks. Sulfur hexafluoride gas (SF_6) is commonly used as a tamponade agent in PR. Perfluoropropane gas (C_3F_8) is more expansible and has a longer duration of action compared to SF_6.[1,2] Therefore, C_3F_8 may be preferable for the treatment of larger retinal breaks or multiple smaller breaks.

For small breaks, some surgeons prefer to use filtered air rather than gas, as air produces fewer biochemical and structural changes in the vitreous than does either SF_6 or C_3F_8.[1,2] However, because air bubbles do not expand within the vitreous cavity and have a shorter duration of action, the use of filtered air requires a larger-volume injection and, consequently, multiple paracenteses before and after injection to mitigate postinjection elevation in IOP.[1]

1 Sinawat S et al. *Arch Ophthalmol.* 2010;128(10):1243-1247.
2 Hilton GF et al. *Indian J Ophthalmol.* 1996;44(3):131-143.

Advantages

When results are controlled for anatomic configuration, PR has demonstrated rates of final reattachment comparable to those reported in SB and primary PPV,[7,8] although there are no prospective studies directly comparing the three modalities. With judicious case selection, PR offers distinct advantages over SB and PPV.

As an office-based procedure, PR does not use systemic anesthesia or sedation; moreover, it eliminates or reduces the time spent scheduling, waiting for OR and staff availability, and the general discomfort and morbidity associated with surgery. PR also provides a substantial cost benefit, with an estimated cost that is between 25% and 50% of that of PPV and SB (individually or in combination).[9,10]

For scenarios in which PPV or SB surgery is warranted—such as in cases of RRD complicated by PVR of grade C or D—but access to vitreoretinal surgical facilities is limited, PR may maintain macular attachment until the appropriate surgical team and resources can be allocated.

Disadvantages

In addition to patient cooperation with postprocedural head positioning,

successful PR requires a high degree of surgical acumen, aptitude, and experience with indirect ophthalmoscopy and retinopexy. The procedure becomes increasingly difficult when dense cataract, vitreous hemorrhage, or other media opacity obscures the identification of retinal breaks.

The greatest contributor to success in PR is appropriate case selection. Hence, a major limitation to using this safe, low-cost, and well-tolerated office-based procedure is its relative lack of generalizability to all cases of RRD.

Gas bubble displacement. It is not uncommon for the expansile gas bubble to move and displace the vitreous.[4] This displacement may create new breaks or reopen a break that was just treated, either of which may lead to failure of reattachment. Another occurrence unique to PR is the formation of smaller gas bubbles ("fish eggs"),[9] which have the potential to enter the subretinal space through the existing retinal break(s).[4]

Pearl. Proper gas injection technique and careful indirect ophthalmoscopy are essential for preventing formation of fish-egg bubbles. The needle should penetrate the eye perpendicular to the sclera, and at least three-quarters of the needle should be withdrawn prior to injection. This makes it easier for the gas emerging from the shaft to enter the vitreous cavity as a single coalesced bubble. If small bubbles do form, light strokes on the sclera with a cotton-tipped applicator may break the surface tension of the bubbles.

Alternatively, the patient can position his or her head so that the fish-egg bubbles are localized away from the break(s). This will allow for spontaneous coalescence of the bubbles, typically within 24 hours. The patient can then resume appropriate positioning for tamponade of the break(s).

Outcomes

Since the inception of PR more than 30 years ago, its overall single-operation success rate (SOSR) has reportedly increased from 55% to between 75% and 80%,[7,9] likely due to more stringent patient selection by retina specialists. Nevertheless, the SOSR for PR remains lower than the 83% to 85% rate reported for PPV or combined SB/PPV and the 75% to 91% reported for SB.[7,8] This may be attributed in part to unidentified breaks, which are most often the cause of persistent or recurrent RD after PR in appropriately selected cases of uncomplicated RRD.

Given these statistics, a majority of retina specialists often choose to perform SB, PPV, or both instead of PR. However, SOSR should not be the sole criterion in selecting the treatment for uncomplicated RRD. Studies have shown that the rate of final reattachment with surgical intervention or PR in appropriately selected patients is greater than 95%.[11,12] Moreover, performing PR as a first-line treatment eliminates an OR visit, reduces cost to the patient and health care system, and offers the potential for rapid improvement in visual acuity.[3,13]

Reoperation. Even in cases in which an initial failure required reoperation with repeat PR or with SB or combined SB/PPV, patients who had first undergone PR have been reported to achieve better visual outcomes compared with SB alone.[9] We believe this is likely attributable to the potential for earlier macular reattachment, as well as purposeful head positioning, which inhibits further accumulation of subretinal fluid.

Furthermore, the use of PR does not affect the patient's ability to undergo later PPV or SB[9,13]; thus, those failing primary PR treatment remain viable candidates for reattachment with a surgical procedure. The rates for most postoperative complications with PR—including the development of PVR, cystoid macular edema, diplopia, and epiretinal membrane—are equal to or less than that of SB and PPV.[7]

Pearl. If retinal apposition has not been achieved after PR and reoperation with PPV, SB, or both is needed, the patient should be advised to avoid supine positioning in the immediate preoperative setting. Prolonged contact of intraocular gas with the posterior lens surface may cause lens feathering with posterior subcapsular changes,[14] which can contribute significantly to poor intraoperative visibility.

Conclusion

PR is a safe, low-cost, well-tolerated, office-based procedure that is often underutilized. Successful outcome is primarily dependent on a thorough retinal examination that identifies all breaks and on careful patient selection. With these criteria in mind, physicians may opt for PR as a first-line treatment and nonsurgical alternative to SB, PPV, or combined SB/PPV in patients with uncomplicated superior RRD.

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For full disclosures, see this article at aao.org/eyenet.

EXTRA **MORE ONLINE.** Table 1 appears with this article at aao.org/eyenet. See a video of PR at aao.org/clinical-video/pneumatic-retinopexy-rhematogenous-retinal-detachm.

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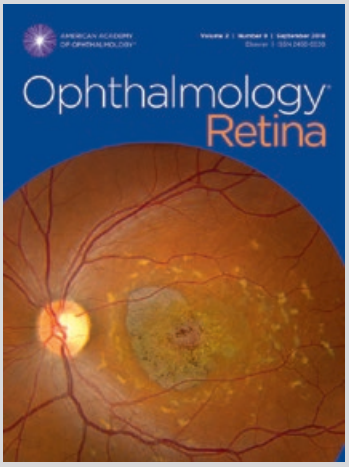

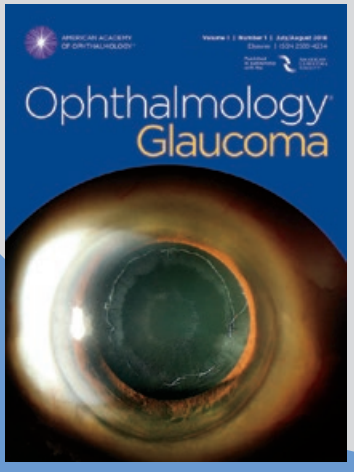

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The Eyelid Lump That Wouldn't Go Away

Ramon Silva,* a 41-year-old personal trainer, had developed a painless, yellowish lump on his right eyelid about 12 months earlier. The lesion was nonprogressive and had no associated discharge. Mr. Silva had visited several physicians for the lump, which was resistant to conservative medical treatment, including warm compresses and several trials of topical antibiotic ointment and steroid ointment. By the time he was referred to our oculoplastics clinic for an opinion, he was frustrated about the lack of improvement in this lesion.

We Get a Look

On examination, Mr. Silva's visual acuity was 20/20, and his intraocular pressure was 16 mm Hg in both eyes. The pupils were equal, round, and reactive, with no afferent pupillary defect. Examination of the conjunctiva, cornea, anterior chamber, and fundus demonstrated no abnormalities.

A firm, yellowish, elevated nodule, measuring approximately 3 × 4 mm, was noted on the temporal aspect of his right upper eyelid (Fig. 1). There was no inflammation, ulceration, bleeding, or discharge. The lid architecture was normal, and we saw no madarosis or telangiectatic vessels. Lid eversion revealed normal-appearing forniceal and bulbar conjunctiva, with no posterior extension of the mass.

His previous ophthalmic history was unremarkable. He had been taking indomethacin and oxycodone-acetaminophen (Oxycocet) since having knee surgery in 2016 for a sports-related injury. Review of systems was negative for skin cancer in our darkly pigmented patient, and Mr. Silva said he had no cutaneous lesions elsewhere.

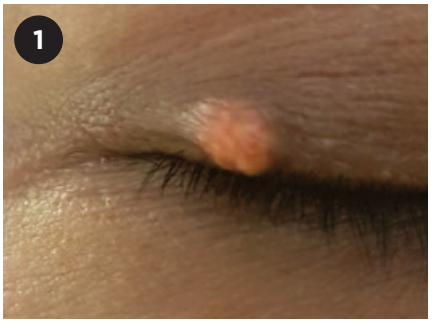
Differential Diagnosis

The lack of erythema and inflammation was not typical of chalazion. The lesion did not have the malignant features or morphology of basal cell carcinoma, squamous carcinoma, or sebaceous carcinoma. The nodule lacked the violaceous hue that is commonly seen in a pilomatrixoma. Subepidermal calcification tends to be less yellow than this patient's lesion. The mottled opacification was not characteristic of epidermal inclusion cyst. Xanthogranuloma was in the differential, but the patient had no other lesions elsewhere.

Further Testing and Biopsy

An incisional biopsy was performed. At the time of the biopsy, the lesion was remarkably dry, gritty, and whitish-yellow. The specimen was submitted to the lab in formalin.

Low-power magnification (4×) of the hematoxylin-eosin (H&E)-stained specimen revealed pale, basophilic amorphous areas surrounded by inflammatory infiltrate composed of lymphocytes, histiocytes, and occasional giant cells. A high-power view (200×) exhibited pinkish aggregates of wispy acellular material surrounded by a palisade of histiocytes and foreign body giant cells (Fig. 2). The pale, basophilic granular material represents a proteinaceous matrix housing needle-like spaces in radial array. These spaces are left behind when urate crystals are dissolved by formalin fixation.



WE GET A LOOK. *The patient presents with a lesion of the upper right eyelid.*

Our Diagnosis

From the histologic appearance of this eyelid lesion, we determined that it was a tophus, which is pathognomonic for gout. This case illustrates an uncommon ocular manifestation of a common systemic disease.

At the follow-up exam three weeks later, the eyelid was completely healed without scarring. Mr. Silva's uric acid level measured at 654 mmol/L (upper limit of normal, 430 mmol/L), but he elected not to take uricosurics, preferring to control his condition with diet and exercise. On direct questioning, Mr. Silva said that he had been diagnosed with gout a few years earlier.

BY **JUSTINE PHILTEOS, BA, HARLEEN BEDI, HBSC, MD,** AND **EDSEL ING, MD, FRCSC, MPH, CPH.** EDITED BY STEVEN J. GEDDE, MD.

Edsel Ing, MD, FRCSC, MPH, CPH

Discussion

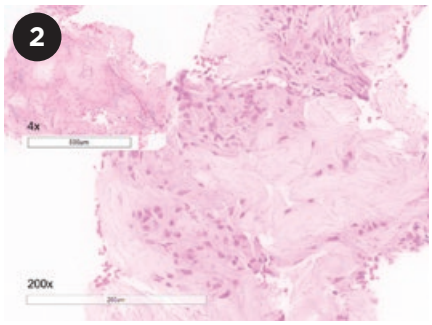
Gout is the most common inflammatory arthritis, characterized by the abnormal deposition of monosodium urate crystals in and around joints such as the metatarsophalangeal joint of the hallux (podagra). The crystals may also be deposited in the skin as potentially disfiguring subcutaneous tophi.

Risk factors for gout include male sex, age, and obesity. Impaired renal excretion of uric acid, overproduction of uric acid, and excess dietary intake of purines contribute to the pathophysiology of this crystalline arthropathy.

Gout is associated with metabolic syndrome, cardiovascular disease, and renal disease. Although gout was traditionally considered a disease affecting only the affluent, that is no longer true because of the increasing trend in obesity.

Gout and the eye. Although gout is a very common disease with an estimated prevalence of up to 4% in North America,[1] eyelid tophi are a rare manifestation. Our review of literature found only six other cases of tophaceous gout of the eyelid (Table 1).[2-7] The average age at presentation was 50 years, with a median age of 44 years. There was a marked male predominance, which is consistent with the epidemiology of gout.

The patients with eyelid manifestations had preexisting gout ranging from three to 20 years. All cases developed yellowish or whitish tophi in the upper lid or canthi. Four of the six patients reported associated gouty arthropathy involving the first metatarsal, elbow, ankle, and finger joints.



HISTOLOGY. *Fragments of fibrous tissue studded with basophilic, acellular wispy material associated with a brisk inflammatory infiltrate composed of lymphocytes, histiocytes, and occasional multinucleated giant cells, with an intact epithelium (hematoxylin-eosin stain, inset ×4, high-power section ×200). The pale, basophilic granular material represents the proteinaceous matrix housing needlelike spaces in a radial array. These spaces represent outlines of dissolved urate crystals after formalin fixation.*

Tophi are pathognomonic of gout. In addition to eyelid tophi, other ophthalmic manifestations of gout include orbital tophi, persistent subconjunctival hemorrhage, corneal crystals, and uveitis.[8]

Systemic associations with tophi. The development of tophi corresponds with early age of gout onset, longer duration of hyperuricemia, and higher serum urate levels. Tophaceous lesions usually develop in patients after 10 years of hyperuricemia. However, tophus formation may occur sooner in individuals with myeloproliferative disorders, chronic renal disease, and long-term diuretic use, as well as those with early-onset gout. An isolated normal uric acid level does not exclude the diagnosis of gout, just as an elevated uric acid level is not diagnostic of gout. Occasionally, gout may be triggered by a rapid drop in uric acid levels, and up to 30% of men with gout may have low or normal uric acid levels at the time gout symptoms present.[9]

Biopsy tips. Alcohol is the ideal fixative for preservation of gout crystals because they are soluble in formalin and water. Although formalin dissolves uric acid crystals, the needlelike spaces seen on H&E, as in our patient, are often diagnostic. Ancillary studies are required only if there is an inadequate amount of tissue, a paucity of crystals, or an unusual histologic appearance.

If gout is suspected and the characteristic needlelike spaces are not seen on conventional formalin-fixed H&E preparation, staining with nonaqueous alcoholic eosin or Carnoy fixative can be done to preserve the sodium urate monohydrate deposits. Birefringent crystals can be subsequently visualized under a polarizing microscope, revealing negative birefringence (yellow color) when the long axis of the crystal

TABLE 1. Case Reports of Eyelid Tophi

Author	Age (years)	Sex	Duration of gout (years)	Duration of lesion	Location of lid lesion	Lesion size (mm)	Other lesions
De Monteynard[2]	62	F	-	2 days	Lateral canthus	-	-
Morris[3]	44	M	-	1 year	Lateral canthus	6 × 5 × 4	-
Yen[4]	27	M	3	3 months	Medial canthus	11 × 5 × 5	1st metatarsal (MT)
Jordan[5]	68	M	20	2 years	Medial canthus	5 × 6 × 4	Elbow
Yang[6]	64	M	-	9 years	Middle upper lid	14 × 10 × 8	Fingers
Nakatsuka[7]	41	M	10	1 year	Lateral canthus	4 × 7 × 4	Ankle, 1st MT
Present case	41	M	3	1 year	Temporal upper lid	4 × 5 × 4	Knee? (no surgical specimens were sent to pathology for gout)

Jonathan H.C. Lai, MD

is oriented parallel to the polarized light. If the specimen has already been submitted in formalin for less than 12 hours, an unstained coverslip technique with 10-µm thick slides can sometimes reveal negative birefringence.

Classification. The 2015 American College of Rheumatology and European League Against Rheumatism (ACR-EULAR) gout classification criteria are the most widely used for diagnosis of gout. The 10 criteria include history, clinical examination, uric acid level, laboratory results, and radiologic findings to predict the likelihood of an acute gout flare.[10]

Although tophi are mentioned in the ACR-EULAR document, the ocular adnexal location is notably absent. Despite the rarity of a tophaceous lesion in the eyelid, it is important to be aware of this atypical manifestation of a common systemic disease to expedite diagnosis. When faced with a nonresolving eyelid lump, the clinician should consider a biopsy. A periocular tophus could be the precursor of a painful systemic disease and subclinical renal dysfunction.

Conclusion

Eyelid lesions can point to the diagnosis of systemic disease. Ophthalmologists should be aware of the ophthalmic manifestations of gout,[8] which may be the initial presenting sign of poorly controlled hyperuricemia. Tophaceous gout should be in the differential diagnosis if a middle-aged patient, usually male, presents with a nonulcerated, yellowish-white lid lesion, especially if it is gritty and dry at the time of biopsy. Patients should be asked about a preceding history of gouty arthritis, particularly podagra. If gout is suspected, the specimen is ideally submitted in alcohol because the crystals are soluble in formalin.

*Patient name is fictitious.

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Ms. Philteos is a medical student, **Dr. Bedi** is an ophthalmology resident, and **Dr. Ing** is associate professor and specialist in oculoplastics, strabismus, and neuro-ophthalmology. All are at the University of Toronto in Toronto, Ontario, Canada. *Financial disclosures: None.*

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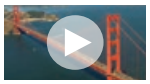

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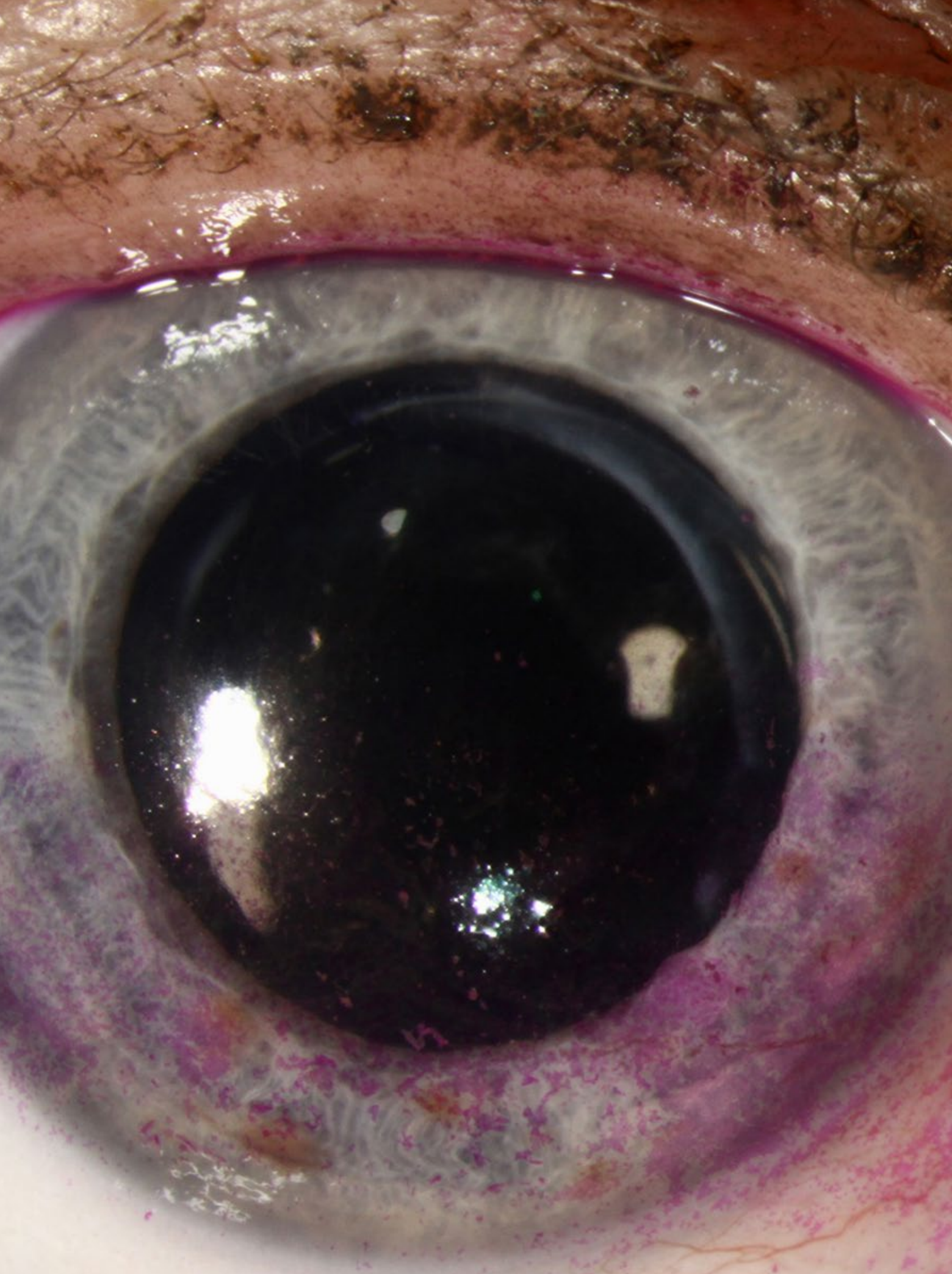

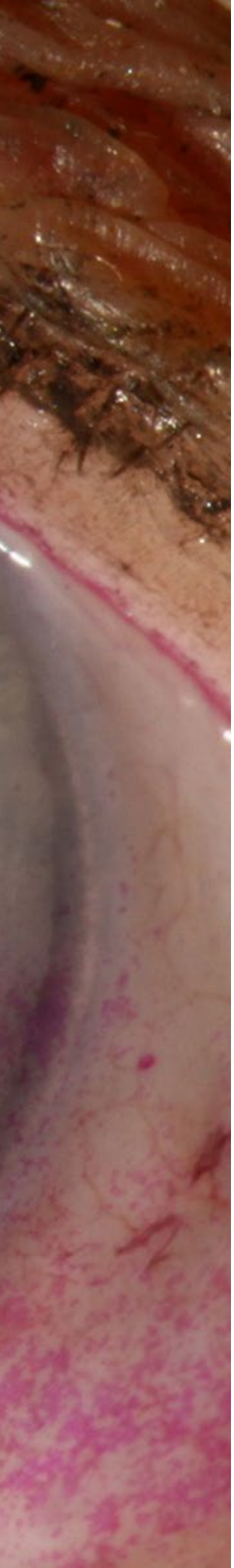

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Managing Dry Eye Disease, Case by Case

Five dry eye experts share their insights on diagnostic approaches and therapeutic modalities—new and old—for this difficult, multifaceted disorder.

By Gabrielle Weiner, Contributing Writer

When it comes to treating dry eye disease (DED), some ophthalmologists may be skeptical of the hype surrounding the latest drugs and devices to hit the market. They caution that until there is a better understanding of DED's underlying mechanisms, therapeutic and diagnostic breakthroughs may remain elusive.

Still, ophthalmologists with an interest in dry eye have reasons for optimism. Dry eye experts are noting incremental advances in diagnosis and treatment in their daily practices. "From my perspective, there have been major improvements already," said Elisabeth M. Messmer, MD, at Ludwig-Maximilian University of Munich in Germany.

Update on Therapies

Innovations. According to Dr. Messmer, today's artificial tears include ingredients that enable them to remain longer on the ocular surface. These include compatible solutes (osmoprotectants), lipids, and molecules that work as secretagogues. Even more important, artificial tears without the toxic preservative benzalkonium chloride are now readily available, she said.

Penny Asbell, MD, at the University of Tennessee Health Science Center in Memphis, reported that new molecules to replace missing elements in the tears, such as proteoglycans, and novel antioxidative drugs, such as SkQ1, are coming down the pike. In particular, Giacomina Massaro-Giordano, MD, at the University of Pennsylvania in Philadelphia, is excited about a glycoprotein lubricant called lubricin, which is different from carboxymethylcellulose and all previous lubricants. She is also optimistic about a synthetic form of lacritin—a protein that is selectively deficient in dry eye tears and stimulates tear secretion and corneal epithelial renewal. In addition, nerve growth factor drops (cenegermin, Oxervate), recently FDA approved for neurotrophic keratitis, may help a subset of dry eye patients.

Anti-inflammatories. Anti-inflammatory drugs on the market include cyclosporine A (Restasis, CSA 0.05% in the United States; Ikervis, 0.1% in Europe) and lifitegrast (Xiidra). There is a role for these medications, though the benefits depend on careful patient selection, according to Sonal S. Tuli, MD, MEd, at the University of Florida in Gainesville. For starters, most patients with inflamed eyes cannot tolerate the drops. "To make cyclospo-

rine into an emulsion, you have to make it a little acidic," Dr. Tuli explained. "It can feel like putting lemon juice on a wound." To help patients tolerate Restasis or Xiidra, most clinicians first prescribe steroids to calm the eye, according to Joanne F. Shen, MD, at Mayo Clinic in Arizona, who is not a fan of the so-called Lotemax-to-Restasis bridge. "Once patients start on steroids, they don't want to come off. Many patients will need cataract surgery earlier than would have been expected [because the steroid can cause cataract formation]," she cautioned.

Dr. Tuli sometimes opts to bridge a patient to Restasis with a milder steroid for a week, but she insists on a strict, rapid taper. Both Drs. Tuli and Shen are proponents of doxycycline and often choose to skip the Restasis- or Xiidra-plus-steroid approach.

Newer formulations of cyclosporine (e.g., the combination of cyclosporine with semifluorinated alkanes to improve bioavailability) are in the study pipeline, according to Drs. Messmer and Asbell; results are expected soon. One new nanotechnology formulation, a nanomicellar formulation of cyclosporine A (0.09%) called Cequa was FDA approved in 2018 but is not yet commercially available. Generic versions of CSA were expected to enter the U.S. market last year but have been delayed, said Dr. Tuli.

Devices. Mechanical options are also available to treat meibomian gland dysfunction (MGD), including LipiFlow and intense pulsed light (IPL). An intranasal neurostimulator, TrueTear, is now sold over the counter. Despite the hefty price tag for the latter, Dr. Tuli said that some patients really like it. However, why or how long it will continue to have a sustained effect after its use is discontinued is still unknown, she said.

Diagnostic Considerations

Diagnostic tools. Today, diagnostic tools to detect inflammation (e.g., biomarkers like MMP-9) and corneal innervation are recognized as important for individualizing treatment. Dr. Asbell is most excited about the potential for minimally invasive objective metrics. "The development of well-validated biomarkers would allow us to more specifically categorize DED problems and tailor our treatments accordingly," she said.

Diagnosis is paramount. Often, the takeaway from expert discussions about DED is to spend time performing an exhaustive examination to pin down the cause of dry eye. Therapies can differ completely, depending on whether the etiology lies in the tear film, anatomy, or nervous system—or in a combination of these. Moreover, the cause can have an impact on how aggressive your approach might be. For example, when Dr. Tuli sees patients with Sjögren syndrome, a progressive autoimmune process that will continue to damage their tear glands, she starts them on one of the prescription drugs right away, even if the patient doesn't have symptoms. But she wouldn't be so aggressive for a patient with dry eye induced by computer use.

Make the time for workup. According to Dr. Shen, it's extremely difficult in most practices to find the time needed to rule out everything that could be masquerading as dry eye or contributing to it. Dr. Massaro-Giordano agreed and emphasized the importance of conjunctival staining, especially with lissamine green. Dr. Messmer added, "With a drop of fluorescein, you can judge three important things at the same time to establish a dry eye diagnosis: 1) the tear film meniscus, 2) tear film break-up time [TBUT], and 3) ocular surface damage."

Make time for patient interaction. The experts advise ophthalmologists to set aside adequate time for dry eye patients. "Show your patients some love," said Dr. Asbell. "Listen to them carefully and see them regularly if they're very symptomatic." Dr. Messmer added, "Take your patients' complaints seriously. Some may complain of visual disturbances although they have full vision on conventional vision testing. This is due to a decrease in functional visual acuity."

Looking Ahead

Some ophthalmologists have developed a healthy level of skepticism about new products. But, said Dr. Massaro-Giordano, given the vast number of DED patients and the many therapies in development to address different mechanisms and symptoms, it's important for ophthalmologists to keep a keen eye on the pipeline and an open mind.

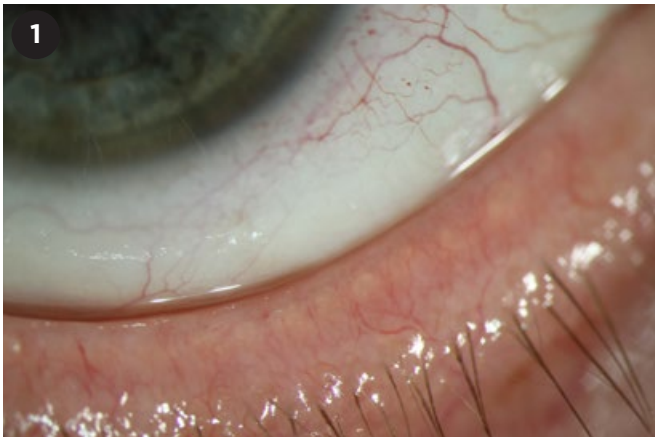
"It's hard to say why some things work for dry eye," said Dr. Massaro-Giordano, "They just do. Over 25 years, I've seen it clinically, though sometimes it's hard to pinpoint the science behind it." For those waiting for evidence on whys and hows of various treatments, she said, "The science is coming!"

Case Studies

The cases on the next few pages help elucidate the diagnostic process and therapeutic approaches—often combining newer therapies with the trusted standbys—followed by experts in the field. The key messages are recognizing that DED is a multifactorial process, tailoring treatment to the particulars of the individual case, and being prepared to escalate to more intensive therapy when response is inadequate.

CASE 1:
Neuropathic Ocular Pain, or "Pain Without Stain"

A 55-year-old woman presents with symptoms of "burning" eye discomfort, light sensitivity, and occasional pain that has been recalcitrant to aggressive lubrication and topical steroids. Visual acuity (VA) with spectacle correction is 20/20 in both eyes. There is mild MGD in both sets of eyelids, but the rest of the ocular and eyelid examination is within normal limits. Schirmer testing is 7 mm bilaterally.



CASE 1. *Mild meibomian gland dysfunction.*

DR. SHEN. I follow a variation of the DEWS II diagnosis and treatment algorithm. In my EHR, I have added a list of questions to ask about symptoms of nocturnal lagophthalmos (dry eye worse upon awakening in the morning) and to rule out other types of ocular surface disease (OSD; e.g., autoimmune diseases such as graft-vs.-host disease or rosacea, lagophthalmos, and recurrent or past severe eye infection) or mechanical reasons for poor blink function (e.g., Parkinson disease, cosmetic surgery, or use of Botox or fillers).

This patient has an Ocular Surface Disease Index (OSDI) score of 66, so I have a baseline to compare to future visits. Neither fluorescein nor lissamine green stain reveals any significant findings on the cornea or conjunctiva. With a thorough slit-lamp exam, I always evert the eyelids to look for other OSD culprits. This patient shows no staining, foreign bodies, concretions, scarring, or papillary or follicular conjunctivitis. To check IOP, I have the technician use an iCare tonometer to avoid instilling anesthetic that could affect the staining. Bilateral corneal sensation is confirmed by touching the cornea with a wisp of cotton. After I place topical anesthetic, the eye discomfort improves only 50% in both eyes.

With no ocular surface findings and severe burning pain symptoms, along with incomplete relief of pain with topical anesthetic, the DEWS II diagnostic algorithm indicates that the patient has either "symptoms without signs" or "neuropathic pain." I follow the staged treatment steps outlined in DEWS II. (See page 45.)

The patient's MGD is very common and is not a likely cause of her symptoms. Since it is easy, cheap, and low risk, I advise Step 1 treatment. I would also talk to the patient about neuropathic eye pain and how it differs from DED, reassuring her that, fortunately, I don't see severe damage on the clinical exam. If there is access to laser in vivo confocal microscopy, corneal subepithelial nerve plexus imaging would likely show microneuromas, decreased nerve density, and increased tortuosity.[1]

I would also try DEWS II Step 2 therapy, low-dose topical steroids and punctal plugs, if the tear meniscus is low and there is no history of reflex tearing.

If plugs plus steroids did not help, I would then consider the following measures: autologous serum tears (AST) 20% every two hours for six months with low-dose steroids (I try to defer use of AST because of their out-of-pocket expense) and future placement of Prokera (biotissue); pain medications and referral to a pain specialist for the neuropathic eye pain; an FL41 filter (in case of light sensitivity) or moisture chambers; and lastly scleral lenses.

DR. MASSARO-GIORDANO. Neuropathic ocular pain has confounded ophthalmologists for many years. Many patients with neuropathic pain are dismissed by their doctors when, in fact, they are some of the most devastated patients and they need special care.

In addition to Dr. Shen's list of medications to consider, I might add low-dose oral naltrexone 2 mg, an opioid antagonist.[1] I would also note that, in my clinical experience, scleral lenses do not work as well if the pain has become centralized.

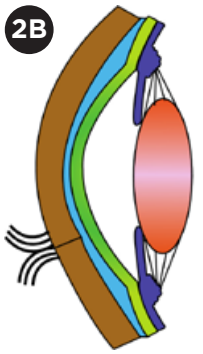
CASE 2:
Exposure Keratopathy

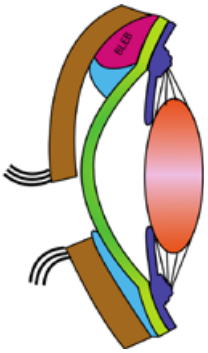
An 89-year-old man with primary open-angle glaucoma presents with unilateral eye pain, redness, and fluctuating vision in the right eye. The other eye is not symptomatic. VA is 20/60 in the right eye and 20/25 in the left. He has had a trabeculectomy in the symptomatic eye. He uses a prostaglandin analogue and an alpha

Anat Galor, MD, MSPH

agonist in both eyes. Examination reveals mild generalized conjunctival injection, an elevated superior bleb without localized injection, and diffuse inferior corneal staining in the right eye. The elevated bleb causes incomplete eyelid closure. The left eye has scattered areas of punctate staining throughout the cornea. There is bilateral MGD. Schirmer testing with anesthesia is 12 mm in both eyes. TBUT is 6 seconds bilaterally.

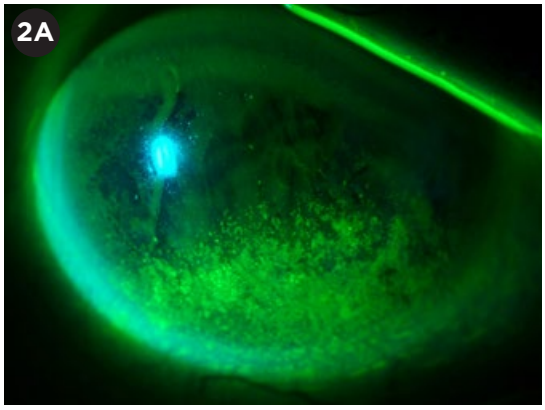
DR. TULI. Glaucoma treatment and dry eyes have a well-established relationship, primarily because of toxicity from glaucoma drops. However, ocular surface changes caused by glaucoma surgery are now increasingly recognized. Both trabeculectomy and tube shunt surgery are associated with an elevated area near the limbus resulting from the filtering bleb or the patch graft over the tube. This elevation can lead to several problems with tear physiology. As with this patient, a high bleb can cause incomplete closure of the eyelid, resulting in exposure keratopathy.





Another reason for ocular surface instability is defective wiper action of the upper lid, leading to inadequate spread of the tear film, stagnation of tears under the bleb, and rapid TBUT (Fig. 2B). This dysfunction can also lead to the formation of dellen and filaments under the bleb.

Management of these patients is challenging. Bleb management early in the postoperative period is critical to minimize the risk of a very high and cystic bleb. In addition, patients with trabeculectomy blebs are advised against having procedures that may shorten the upper lid such as blepharoplasty and ptosis surgery.



CASE 2. *Diffuse inferior staining.*

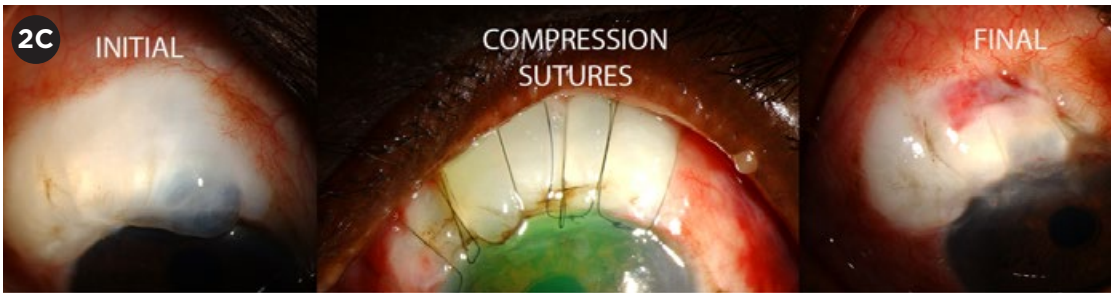
Plugging the lacrimal canaliculi and having the patient use supplementary tears can increase the tear lake and mitigate the drying of the cornea in the area of exposure keratopathy. Patients are asked to use a lubricating ointment at night, when the exposure is particularly problematic. Moisture chamber glasses can help by improving the humidity of the air around the eye.

Filamentary keratitis is managed with debridement and hypertonic saline ointment at night or acetylcysteine eyedrops. However, patients with this condition often require surgical management to resolve the OSD. One strategy is to decrease the bleb height with compression sutures (Fig. 2C).

DR. MASSARO-GIORDANO. In my experience, switching patients to preservative-free single-use glaucoma drops can make a significant difference. Although these drops are more expensive, and often a prior authorization from the insurance company is required, I recommend making the extra effort.

I agree with telling patients to use lubricating ointment at night, though I prefer gels. If a patient's eyes do not close, I recommend that they use disposable bubble eye bandages such as NitEye at bedtime.

Also, keep in mind that patients who need surgery might be candidates for microshunt glaucoma devices placed in the eye so there are no surface issues. Finally, be sure to treat the MGD to help the overall tear film.



DEWS II: Staged Management and Treatment Recommendations for Dry Eye Disease

Step 1

- Education regarding the condition, its management, treatment, and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

Step 2

If above options are inadequate, consider:

- Nonpreserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage DED[1]
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited duration)
- Topical secretagogues
- Topical nonglucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3

If above options are inadequate, consider:

- Oral secretagogues
- Autologous/allogeneic serum eyedrops
- Therapeutic contact lens options
- Soft bandage lenses
- Rigid scleral lenses

Step 4

If above options are inadequate, consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation)

IMPORTANT CAVEATS

- Potential variations within the disease spectrum are acknowledged to exist between patients, and the management options listed above are not intended to be exclusive. The severity and etiology of the DED state will dictate the range and number of management options selected from one or more steps.
- One or more options concurrently within each category can be considered within that step of the dry eye disease state. Options within a category are not ranked according to importance and may be equally valid.
- It should be noted that the evidence available to support the various management options differs and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.

1 The use of prescription drugs needs to be considered in the context of the individual patient presentation, and the relative level of evidence supporting their use for that specific indication, as this group of agents differs widely in mechanism of action.

SOURCE: Jones L et al. *The Ocular Surface* (2017):580e634.

KEY RESOURCES

For a comprehensive discussion of DED management, read the Academy's *Preferred Practice Pattern on Dry Eye Syndrome*, updated in 2018, at aao.org/preferred-practice-pattern/dry-eye-syndrome-ppp-2018.

PDFs of the DEWS II publications and executive summaries that were published in *The Ocular Surface* in 2017 are available at the Tear Film and Ocular Surface Society website at www.tfosdewsreport.org.

CASE 3:
Stain Without Pain

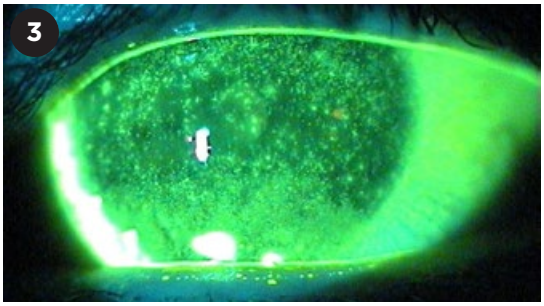
A 65-year-old man with facial rosacea and rhinophyma presents for routine examination, complaining of progressive reduced vision in both eyes over the last two years. He does not note any foreign body sensation. On exam, VA is 20/60 in both eyes. He has severe rosacea blepharitis with diffuse corneal staining bilaterally. TBUT is instantaneous in both eyes, and Schirmer testing is 8 mm bilaterally. He also has bilateral 2+ nuclear sclerotic cataracts and is considering cataract surgery.

DR. MASSARO-GIORDANO. Starting with the patient's history, I ask whether he has a personal or family history of an autoimmune disorder. I ask about dry mouth, sleep apnea and CPAP use, and use of over-the-counter tears with preservatives, which can contribute to corneal staining. I also inquire about current medications, particularly hormonal therapy such as antiandrogens for prostate issues, as this can aggravate MGD.

I assess whether his reduced VA is due to surface disease and/or cataract by checking the refraction and seeing if it improves with correction. I look at the degree of rosacea and consider Demodex infestation, checking for debris on the lids and lashes, specifically waxy collarettes. I characterize the degree of telangiectasia and look at the expressible and nonexpressible meibomian secretions and whether the tears appear foamy.

Staining the conjunctiva and lid margins with lissamine green and looking for a widened Marx line are useful steps. I also carefully examine the tear height to rule out tear insufficiency dry eye (e.g., Sjögren syndrome). In addition, I would check corneal sensation; given the diffuse staining, one would expect some degree of symptoms.

Typically, I obtain LipiView images to look at incomplete blinks and thickness of the lipid layer as well as infrared images of the meibomian glands. I do MMP-9 testing as well, though I do not routinely get confocal images of the glands. However, I do obtain confocal images of the cornea if I suspect corneal nerve abnormality.



CASE 3. *Diffuse corneal staining.*

It's critical to stabilize the tear film and treat inflammation before cataract surgery, even just to get accurate IOL calculations. My approach would start with aggressive lid hygiene. I instruct patients how to safely massage and clean their lids with premoistened pads. If I suspect Demodex, I recommend pads containing tea tree oil. If the patient has difficulty with this regimen, I may recommend LipiFlow and/or IPL treatment. I do recommend preservative-free artificial tears, but not necessarily lipid-containing tears, and a short course of antibiotic/steroid ointment for the eyes and lids. I consider azithromycin drops for the eyes and lids, brimonidine eyedrops (an off-label use currently being studied), and oral doxycycline or azithromycin. Adding a bedtime ointment or gel is helpful. If Demodex is severe, I add ivermectin cream or tablets.

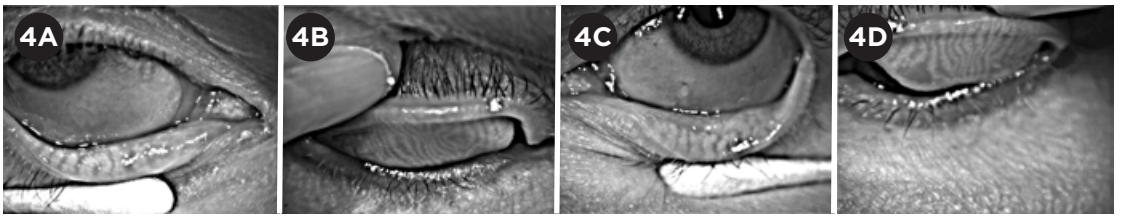
I routinely discuss environmental triggers, such as heat, air vents, and fans, and I suggest use of goggles, humidifiers, etc. When outdoors, patients may benefit from wraparound sunglasses, with or without moisture chambers. Blinking exercises and appropriate tablet/computer use are also reviewed. If a patient asks about omega-3 fatty acids, I discuss the current evidence.[2]

It's worth noting that rosacea is complicated, and its mechanisms are not clearly understood. There is some debate over whether more telangiectasia truly equals worse MGD, and my sense is that there is a correlation. A recent paper used lid injections of bevacizumab for MGD and saw good results with diminished vascularity.[3]

CASE 4:
Post-LASIK Dry Eye

A healthy 38-year-old man who works as a financial analyst presents with fluctuating vision and foreign body sensation in both eyes. He underwent bilateral myopic LASIK six months ago. He is not using any drops. On exam, uncorrected VA is 20/25^{-1} in both eyes, improving to 20/20 with pinhole. LASIK flaps are unremarkable, but the corneas have moderate epithelial staining bilaterally. Schirmer testing is 6 mm, and TBUT is 8 seconds in both eyes. Corneal topography reveals a well-centered myopic LASIK, but the Placido rings are not crisp.

DR. SHEN. Based on the patient's surgical history, I am most concerned about relatively neurotrophic



post-LASIK dry eye. A refraction is performed to ensure he is not overminused or demonstrating presbyopia, but no glasses should be prescribed until his ocular surface is healed. I follow a variation of the DEWS II diagnosis and treatment algorithm and use a list of questions I keep in my EHR to rule out other OSD or mechanical reasons for poor blink function.

The patient's OSDI score is 22. Lid eversion shows no staining, foreign bodies, concretions, scarring, or papillary or follicular conjunctivitis. Corneal sensation is markedly decreased in both eyes when tested before instillation of anesthetic. Topical anesthetic improves 100% of the mild foreign body sensation in both eyes.

LipiView I (Figs. 4A-4D) and Oculus Keratograph5 infrared meibography are performed. LipiView demonstrates a low lipid tear layer, worse in the right eye, and 100% incomplete blinks during the recording (partial blinks, PB). The Keratograph shows some shortening and atrophy of the meibomian glands as well as glands that are engorged with meibum. The patient and I discuss his incomplete blinks and the resulting relative lagophthalmos, compounded by long hours on the computer for his work, with incomplete blink leading to an unstable ocular surface.

Overall, I think the patient is neurotrophic with decreased corneal sensation from LASIK and has MGD compounded by incomplete blinks. It is hard to say why and when the incomplete blinking originated. It is seen commonly in current and previous contact lens wearers.

DEWS II Step 1 treatment for MGD is initiated. I find punctal plug occlusion helpful for incomplete blink and neurotrophic dry eye. The patient may also benefit from LipiFlow (Step 2). Since he is recently post-LASIK, I would recommend three-month dissolvable punctal plugs bilaterally in the lower lids, as his neurotrophic problems may improve with time. We would also discuss nighttime lubricating gel or ointment if symptoms are worse upon awakening.

DR. TULI. I completely agree with Dr. Shen's diagnosis and management plan. The only difference in my approach is that I am a lot more aggressive with dry eye and MGD treatment, especially post-LASIK. I find that these patients have much more significant visual disturbances and are much more unhappy with their outcomes if they have dry eye. I would add higher-level MGD treatment with doxycycline and Restasis and also recommend longer-acting plugs. Since the patient is still symptomatic after six months, it suggests that his issues are likely to be long term. If the above treatments are not sufficient, I would also consider a short course of autologous serum tears or self-retaining amniotic membranes in these patients with a neurotrophic component to their dry eye.

CASE 5:
Dry Eye Secondary to Sjögren Syndrome

A 54-year-old woman with a 20-year history of rheumatoid arthritis (RA) is referred by her rheumatologist for evaluation. She notes reduced vision and chronic discomfort bilaterally. She is currently using preserved artificial tears every hour without relief. She is on disease-modifying therapy for her RA, which is under good control systemically. On exam, VA is 20/40 in both eyes. There is virtually no tear lake. The cornea has diffuse staining with occasional filaments. Schirmer testing is 0 mm. The rest of the exam is unremarkable.

DR. ASBELL. This is classic dry eye disease with severe aqueous deficiency in the setting of a systemic immune-mediated disease, RA. Further examination would include documentation of the degree of OSD. For the cornea, this would entail vital dye testing with fluorescein using a Wratten #12 yellow filter handheld in front of the oculars as you observe the cornea with cobalt blue light to enhance visibility of the staining. For the conjunctiva, lissamine green would be used primarily to enable evaluation of response to treatment over time. The HD Analyzer can be helpful to distinguish between vision loss from OSD and cataract. The former is manifested by wave changes over time, between blinks, and the latter by a wave that is constant between blinks. It is likely that both surface disease and cataracts are contributing to reduced vision in this patient.

Although we have a pretty good idea why

Joanne F. Shen, MD

patients with Sjögren syndrome have dry eyes—inflammatory effects on the lacrimal gland—it is also good to look for MGD, which can contribute to surface changes and discomfort. It's important to gently evert the lid to observe the puncta of the meibomian glands and, with slight pressure, look at the meibum: Are the glands obstructed? Is the meibum cloudy or pasty? If MGD is present, treat it in addition to treating the ocular surface directly. Check also for lid lag and exposure.

Unfortunately, with a Schirmer test of 0 mm, it is unlikely that stimulation will increase tears, so my efforts are mainly geared toward replacing the lubrication and keeping it on the eye. That said, I often do try immunomodulators, including topical cyclosporine or lifitegrast. Even these severe cases sometimes respond to low-dose topical steroid, such as nonpreserved dexamethasone 0.01% drops twice daily (compounded, off-label use). Unfortunately, systemic immunosuppression and/or modulation do not appear to be effective for ocular findings, likely because the lacrimal gland is already too severely damaged to respond.

For lubrication, only nonpreserved treatments are recommended. A thicker consistency, such as gels and ointments, may work better. Compounded autologous serum can be helpful, though strong evidence is sparse, and these drops can be costly and require careful attention to hygiene to avoid contamination. Punctal occlusion can be considered and may help keep the lubricants on the ocular surface for longer contact.

If filamentary keratitis is present, filament removal at the slit lamp can be a short-term fix and is especially helpful if lubrication is then maximized. Amniotic membrane with a bandage contact lens is sometimes useful for severe flare-ups, but it is not practical for this chronic condition. For both symptoms and vision, contact lenses may be needed. Occasionally, a soft bandage lens can help, but more typically scleral lenses, with their reservoir of fluid, are the only way to achieve clinical improvement.

DR. TULI. Sjögren syndrome patients can be very challenging, especially those who have an almost complete absence of aqueous tears. I explain to these patients that even preservative-free artificial tears should not be used every hour, as they can deplete the mucins that act as conditioners of the ocular surface to allow the tears to adhere to the eyes. In severe dry eye patients, secretagogue medications such as oral pilocarpine or cevimeline may be helpful—however, they stimulate salivary glands more than lacrimal glands and therefore work better for dry mouth. Finally, I stress the need to use topical cyclosporine chronically, even if patients do not perceive any benefit for their symptoms. The lacrimal gland damage that occurs in Sjögren syndrome is primarily due to lymphocytic infiltration, and the cyclosporine may mitigate further damage.

1 Dieckmann G et al. *Ophthalmology*. 2017;124(11):S34-S47.
2 Dry Eye Assessment and Management Study Research Group. *N Engl J Med*. 2018;378:681-1690.
3 Jiang X et al. *Drug Des Devel Ther*. 2018;12:1269-1279.

Meet the Experts





Penny A. Asbell, MD, FACS Barret G. Haik Endowed Chair of Ophthalmology; director of the Hamilton Eye Institute; and professor of ophthalmology at University of Tennessee Health Science Center in Memphis. *Disclosures: Allergan: C; Bausch + Lomb: C,S; Contact Lens Association of Ophthalmologists: C; MC2: C,S; Medscape: L; MioTech: C,S; NEI: S; Novartis: C,S; Oculus: L; Office of Dietary Supplements-NIH: S; Rtech: C,S; Santen: L; Scientia CME: L; Shire: C; Vindico: L.*

Giacomina Massaro-Giordano, MD Codirector of the Penn Dry Eye & Ocular Surface Center; professor of clinical ophthalmology at the Scheie Eye Institute at the University of Pennsylvania in Philadelphia. *Disclosures: Celularity: C; GlaxoSmithKline: C; PRN Physician Recommended Nutriceuticals: O.*

Elisabeth M. Messmer, MD Professor of ophthalmology at the Ludwig-Maximilian University of Munich in Germany. *Disclosures: Alcon: C,L; Allergan: C,L; Dompé: C,L; Santen: C,L; Shire C,L; Sun Pharmaceuticals: C; Thea: C,L; TRB-Chemedica: C,L; UrsaPharm: L; Visufarma: C,L.*

Joanne F. Shen, MD Assistant professor of ophthalmology, chair of ophthalmology, and director of the Dry Eye Clinic at the Mayo Clinic in Arizona. *Disclosures: None.*

Sonal S. Tuli, MD, MEd Chair of ophthalmology at the University of Florida, Gainesville. *Disclosures: None.*

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Coding for Eye Injuries, Part 1: When to Use Codes 99050-99060

Many practices treat eye injuries on a weekly, if not daily, basis. Make sure you are coding them appropriately by reviewing this two-part series, which includes one case study below and two more next month.

Check your commercial payers' policies on the 99050-99060 family of CPT codes. Some commercial payers will reimburse you for the codes listed below in addition to the appropriate level of E&M or Eye visit code. First published in 1993, these codes were initially designed for workers' compensation emergency visits.

99050 *Services provided in the office at times other than regularly scheduled office hours, or days when the office is normally closed, (e.g., holidays, Saturday or Sunday), in addition to basic service*

99051 *Service(s) provided in the office during regularly scheduled evening, weekend, or holiday office hours, in addition to basic service*

99053 *Service(s) provided between 10:00 p.m. and 8:00 a.m. at 24-hour facility, in addition to basic service*

99056 *Service(s) typically provided in the office, provided out of the office at request of patients, in addition to basic service*

99058 *Service(s) provided on an emergency basis in the office, which disrupts other scheduled office services, in addition to basic service*

99060 *Service(s) provided on an emergency basis, out of office, which disrupts other scheduled office services, in addition to basic service*

Commercial payers may cover some of the above codes but not others. For each of these six codes, a commercial payer's policy may be to 1) pay for it (though there may be conditions that need to be met), or 2) indicate that payment is the patient's responsibility, or 3) state that it is included in the exam per CMS policy. For example, some commercial plans may cover CPT code 99050 " … in situations that would otherwise require more costly urgent care or emergency room settings … ."

Some commercial payers reserve Eye visit codes for vision exams. For these payers, consider reporting the appropriate level of E&M code when evaluating injuries. The E&M codes also should be considered when MD-patient face-to-face time is a factor.

Don't bill codes 99050-99060 to Medicare Part B or Medicaid. They are factored into the payment of the exam.

Case #1: A Mowing Mishap

When 11-year-old Ronnie* was mowing the lawn, a piece of wire "flipped up" and hit him in the right eye.

Exam. There was a right lower canalicular laceration.

Staff action. Staff told the ambulatory surgery center to add an emergency case that night. They also contacted the insurance company for authorization of three possible surgical codes: For conjunctivorhinostomy, there are two CPT codes, depending on whether or not a tube is inserted (68750 and 68745, respectively); a third option was 68700 *Plastic repair of canaliculi.* First thing the next morning, staff got back in touch with the insurance company to confirm that they could bill 68750 for surgery with tube insertion.

Documentation. Ronnie's chart documented the following: comprehensive history, obtained through his mother; all 12 elements of the exam, through dilated pupils, plus mental assessment; and low-complexity medical decision-making.

CPT codes. The practice billed 99203–57 for the eye exam and 68750–RT for the procedure.

Modifiers. Because the procedure has a 90-day global period, modifier –57 was used to indicate that the exam was performed to determine the need for the major surgery. As not all commercial plans recognize –E4 *Lower right lid,* modifier –RT was used.

Diagnoses. ICD-10 codes: S01.111A *Laceration without foreign body of right eyelid and periocular area* and W228. XXA *Striking against or struck by other objects, initial encounter.*

The rest of the story. Tube removal was done in the office within the 90-day global period and was considered part of the postoperative care. If it had been removed outside that 90-day period or removed by a different physician, it would have been considered part of the E&M or Eye visit code.

* Patient name is fictitious.

BY **ANTHONY P. JOHNSON, MD,** AAOE BOARD MEMBER, AND **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT.

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Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Highlights of Mid-Year Forum 2019

From April 10-13, approximately 500 Academy members met in Washington, D.C., to discuss some of ophthalmology's key policy and practice management issues with legislators, regulators, and Academy leaders.

Three key sessions were:

Controlling drug spending. A discussion of new policies related to Part B drugs spanned administration, congressional, and industry perspectives. U.S. Rep. Kurt Schrader (D-Ore.), a member of the House Energy & Commerce Committee, discussed congressional initiatives to address the challenges, and Academy Secretary for Federal Affairs **David B. Glasser, MD,** highlighted the Academy goal of ensuring patient access to critical treatments while controlling costs and maintaining incentives to promote pharmaceutical innovations. Dr. Glasser also reviewed the Academy's interactions to date with CMS Administrator Seema Verma, MPH, and Secretary of Health and Human Services Alex Azar II.

Emergency planning. This program addressed the prevalence of fires, hackers, shooters, hurricanes, and other types of disasters. Past President of the Puerto Rico Medical Association **Natalio J. Izquierdo, MD,** detailed the devastating personal and professional losses the islanders experienced due to Hurricane Maria as well as the specific impact on Puerto Rican ophthalmology, including residency programs, clinics, ambulatory surgery centers, research projects, and access to pharmaceuticals. Dr. Izquierdo outlined the response to the disaster by the Academy, the Pan-American Association of Ophthalmology (PAAO), and members of PAAO's leadership development program. Some practices mentioned at the MYF are in the Academy's Emergency Planning and Disaster Preparedness Toolkit at aao.org/MYF19-EPDP.

Creating an inclusive practice. This session focused on how best to communicate with a diverse patient base to improve outcomes and maximize patient satisfaction. Academy Secretary for Online Education **Robert F. Melendez, MD, MBA,** encouraged attendees to consider millennial patients' preferences, such as digital access to ophthalmologists, online reviews, and affordable care. Later in the program, **Denice Cora-Bramble, MD, MBA**, Chief Marketing Officer and Executive Vice President of the Ambulatory & Community Health Services at Children's National, who spoke on cultural competence, gave advice for forming "relationships that supersede cultural differences."

MID-YEAR FORUM 2019. *U.S. Rep. Kurt Schrader (D-Ore.) provided insights on congressional initiatives to control drug spending.* ***Denice Cora-Bramble, MD, MBA,*** *shared insight on delivering culturally competent care.*

View the full Mid-Year Forum report at aao.org/myf.

PubMed Approves *Ophthalmology Retina* for Indexing

The National Library of Medicine has accepted *Ophthalmology Retina* for inclusion in Medline/PubMed. This

AMERICAN ACADEMY OF OPHTHALMOLOGY®

is the first time in 12 years that it has accepted a monthly, print U.S. ophthalmology journal.

"A big thank you to our authors who share their work with a new journal. Additionally, for helping us achieve scientific accuracy, I thank our reviewers and editorial board members," said **Andrew P. Schachat, MD,** editor-in-chief.

Learn more about *Ophthalmology Retina* by visiting www.ophthalmologyretina.org.

ACADEMY RESOURCES

How Does Your Practice Measure Up?

Your financial reports give you an important snapshot of your practice performance, but they don't tell you how you measure up against similar practices. Academy and AAOE members can access two key benchmarking tools that provide powerful comparative analytics for the practice: the AcadeMetrics benchmarking tool and the AcadeMetrics Ophthalmic Salary Survey.

The Academy/AAOE AcadeMetrics benchmarking tool compares your financial data to that of similar practices to help you assess your staffing levels, number of satellite offices, and more.

The AcadeMetrics Ophthalmic Salary Survey tracks specific benchmarks related to optometrist, mid-level provider, and staff salary data to help ophthalmologists benchmark their compensation and benefits packages.

Access the AcadeMetrics tools through links on aao.org/practice-management/analytics.

BCSC Self-Assessment Program Features 1,000 New Questions

Sharpen your clinical knowledge and decision-making skills online while earning Self-Assessment CME credits with the *BCSC* Self-Assessment Program, the only resource with questions and concepts derived directly from the Academy's *Basic and Clinical Science Course*. More than 1,000 new questions have been added since the program's launch last year. Subscribers will automatically receive access to the new questions at no additional charge. Enhancements to the notebook and bookmark features are coming soon.

Subscribe at aao.org/bcsc.

D.C. REPORT

Nationwide Ophthalmic Drug Shortages Emerge

Over the past few months, U.S. ophthalmologists have reported difficulties obtaining the following drugs:

- erythromycin,
- prednisolone acetate,
- atropine, and
- dorzolamide.

Additionally, demand for fluorescein strips continues to outpace supply in the United States.

Persistent drug shortages are among the Academy's top federal advocacy issues. The Academy has been in regular contact with the FDA and drug manufacturers and has encouraged more than 130 lawmakers in Congress to urge the FDA Commissioner to act on this issue. Accordingly, the Academy expects an FDA-convened task force on drug shortages to suggest policy solutions to Congress before the end of the year.

Experiencing a shortage? Email Scott Haber, Academy governmental affairs representative, at shaber@aao.org.

TAKE NOTICE

Support the New Truhlsen-Marmor Museum of the Eye

The Academy is building a new Museum of the Eye at its headquarters in San Francisco. Your donation will support an interactive showplace for ophthalmology and the science of vision in a high-traffic tourist destination. By giving to the museum, you are helping to educate, excite, and inspire the public about the importance of sight.

Help make the museum a success. If you'd like to support the new Museum of the Eye, consider making a one-time gift or a pledge over five years to help reach the $12 million fundraising goal.

In Private Practice? Grants for Peds Big Data Research

There is a June 21 deadline to apply for pediatric ophthalmology research grants supported by the Knights Templar Eye Foundation (KTEF) IRIS Registry Research Fund.

Applicants must be Academy members who are in private practice. If your application is successful, you will be able to use the Academy IRIS Registry database to investigate rare or common eye disease affecting children, and to uncover optimal, real-world approaches to prevention and treatment.

More information online. To learn how to apply for a research grant, visit aao.org/iris-registry/data-analysis/knights-templar-iris-registry-research-fund.

Advice From OMIC: Cataract Surgery Risk Reduction

Cataract surgery is the source of most medical malpractice claims reported to the Ophthalmic Mutual Insurance Company (OMIC).

Many patients undergoing cataract surgery have very high visual goals, especially if they invest their own money to upgrade to specialty IOLs. When the outcome does not match these heightened expectations, patients complain not only to their ophthalmologist, but also to acquaintances, insurance companies, regulatory agencies, and malpractice attorneys.

Reduce your liability exposure. OMIC has recommendations for reducing this risk at https://www.omic.com/cataract-surgery-recommendations/.

Destination AAO 2019

GET READY FOR SAN FRANCISCO • PART 2 OF 6

BEAT THE CLOCK

Registration and Program Available This Month

AAO 2019 will be held Oct. 12-15. Registration opens at aao.org/registration on June 12 for Academy and AAOE members and June 26 for nonmembers. Registration for AAO 2019, which is free for members, includes access to:

- symposia and Spotlight Sessions;
- papers, e-posters, and videos; and
- informal and interactive learning formats.

Register for AAO 2019 and for a Subspecialty Day meeting, buy an Academy Plus course pass, and buy tickets for special sessions—such as AAOE Practice Management Master Classes and Skills Transfer labs—by Aug. 7. Prices for registration, the Academy Plus course pass, and tickets will all increase on Aug. 8.

Program. The AAO 2019 program is available online at aao.org/program search beginning June 12. Information is searchable by day, topic, special interest (such as Young Ophthalmologist), or presenter. The online program contains full course information, including time, location, and abstracts.

Reserve Your Hotel Room

Hotel reservations open June 12 for Academy and AAOE members and June 26 for nonmembers. Group reservations for international attendees are also available.

Find more information, including an interactive map of hotels, at aao.org/hotels.

Fraud alert! Several fraudulent companies, pretending to be associated with the Academy and AAO 2019, may appear in web searches or may have contacted you via email. These companies claim that they can book hotel rooms and/or register you for the Academy's annual meeting, but they are unaffiliated with the Academy. Make sure that you book only through the Academy's website and AAO 2019's official hotel reservation provider, Expovision.

If you are ever in doubt, email meetings@aao.org or call 415-561-8500. You can also contact Expovision directly at aaohotels@expovision.com, or call toll-free from within the United States at 866-774-0487.

EVENTS

Attend the Foundation's Red-Carpet Gala

Get ready for the Academy Foundation's 16th annual Orbital Gala on Oct. 13 from 6:00-10:00 p.m., a night of lights, cameras, and action. At this Hollywood-themed fundraiser, you'll have the rare opportunity to dine in the iconic Palace Hotel, bid on unique silent auction items, and dance the night away to a live band. Black tie is optional; glitz and glam are mandatory.

Buy tickets at aao.org/foundation.

SUBSPECIALTY DAY

Register for Subspecialty Day 2019

Subspecialty Day meetings feature world-renowned ophthalmologists presenting the latest developments and pearls. Dates are as follows:

- **One-day meeting on Friday, Oct. 11:** Refractive Surgery
- **Two-day meeting on Friday, Oct. 11, and Saturday, Oct. 12:** Retina
- **One-day meetings on Saturday, Oct. 12:** Cornea, Glaucoma, Neuro-Ophthalmology, Oculofacial Plastic Surgery, and Pediatric Ophthalmology

Find more information at aao.org/subspecialty-day.

AMERICAN ACADEMY OF OPHTHALMOLOGY®

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Orbital Gala 2019

The Palace Hotel
San Francisco
Sunday, Oct. 13
6 – 10 p.m.

Foundation

Step Into a Glamorous Evening on the Red Carpet

Get ready for the Academy Foundation's 16th annual Orbital Gala, where you'll be awash in a glamorous night of lights, cameras and action. At this Hollywood-themed fundraiser, you'll have the rare opportunity to dine in the footsteps of presidents and kings, amid the historic opulence of San Francisco's iconic Palace Hotel. Bid on one-of-a-kind silent auction items and dance the night away to the live band. Black tie optional, glitz and glam mandatory.

Purchase tickets at aao.org/foundation

6 reasons to switch to OMIC

EXPERIENCE

OMIC has defended far more ophthalmic claims than any other carrier. OMIC's knowledge and familiarity with regard to litigation targeting ophthalmology is unmatched in the industry.

EXPERTISE

OMIC is the only malpractice carrier offering comprehensive ophthalmic-specific education for physicians and their employees with resources designed to help minimize claims and lawsuits.

DEFENSE

OMIC has settled 25% fewer of the claims reported to us than our multi-specialty competitors and OMIC's average indemnity payment is 27% lower than the industry.

PERFORMANCE

OMIC is A (Excellent) rated by A.M. Best and has outperformed multi-specialty carriers in almost all financial benchmarks, including operating, combined and premium-to-surplus ratios.

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OMIC provides 17 regulatory and cyber coverage benefits in the standard malpractice policy at no additional premium.

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OMIC's operating advantage has made possible significantly higher policyholder dividends, averaging a 20.8% return per year during the most recent 5-year period compared to 6.6% for multi-specialty malpractice carriers.

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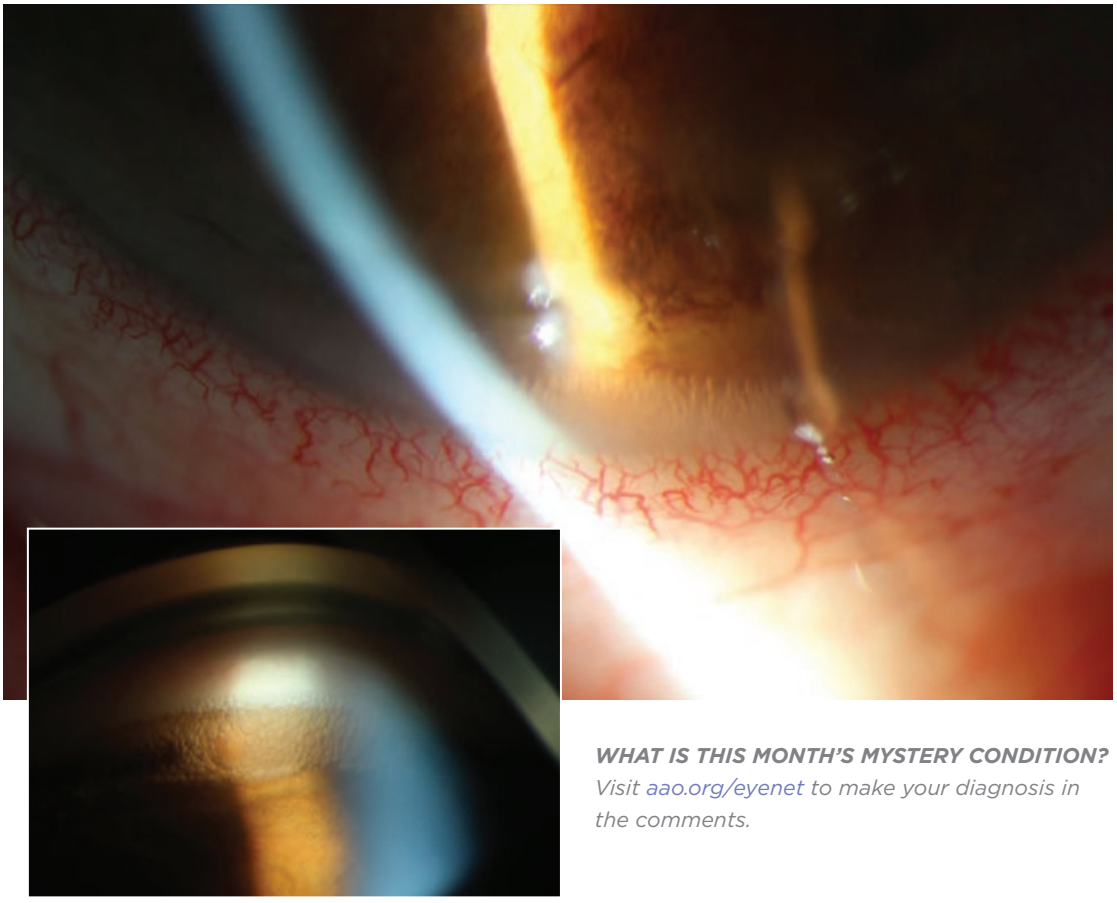
MYSTERY IMAGE

BLINK



WHAT IS THIS MONTH'S MYSTERY CONDITION?
Visit aao.org/eyenet to make your diagnosis in the comments.

Joseph Halabis, OD, Durham Department of Veterans Affairs Medical Center, Durham, N.C.

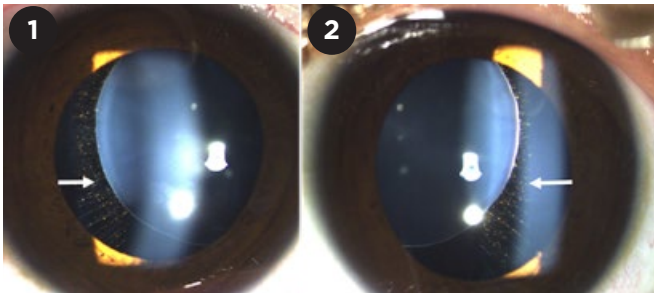
LAST MONTH'S BLINK

Bilateral Ectopia Lentis in Suspected Marfan Syndrome

A 13-year-old girl presented for visual assessment. Her BCVA was 20/30 in both eyes. IOP was 16 mm Hg and 14 mm Hg in the right and left eyes, respectively. The anterior segment examination showed superonasal subluxation of the crystalline lens with visible stretched zonules in both eyes (Figs. 1 and 2). Fundus examination was unremarkable.

Systemic evaluation by the pediatrician revealed features suggestive of Marfan syndrome, including a small forehead, low-set ears, long triangular face with malar hypoplasia, microstomia, peaked nose, and high-arched palate with disorganized teeth. She had mild mitral valve and tricuspid valve regurgitation and bilateral conductive hearing loss. Homocystinuria and Weill-Marchesani must also be considered in the differential diagnosis of ectopia lentis in a young person.

Because the patient had VA of 20/30, without anisometropia, significant astigmatism, or complications related to subluxated lenses (such as cataract, glaucoma, uveitis, or retinal detachment), her physicians determined that she did not require immediate treatment. She will receive regular ocular and pediatric follow-up to monitor for progression.



WRITTEN BY **NITIN K. MENIA, MS, REEMA BANSAL, MS,** AND **SANDEEP BANSAL, MS.** PHOTOS BY **ARUN KAPIL.** ALL ARE AT ADVANCED EYE CENTRE, POST GRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH, CHANDIGARH, INDIA.

LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

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

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

8.4 Pediatric Use
The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

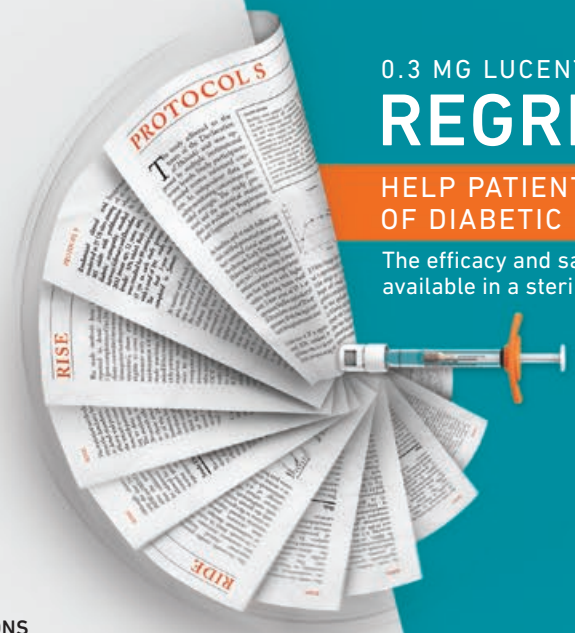
8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017



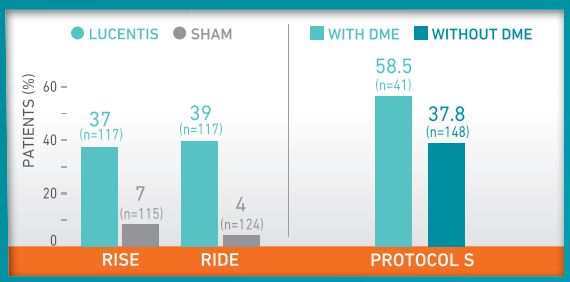
0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED[1]

HELP PATIENTS TURN BACK TO AN EARLIER STAGE OF DIABETIC RETINOPATHY (DR)[1]

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a sterile glass prefilled syringe.[1]

≥2-STEP IMPROVEMENTS AT 2 YEARS[1]*



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

RISE AND RIDE
- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S
- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).[1]

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
- Diabetic retinopathy (DR)
- Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

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

*The following clinical trials were conducted for the **DR & DME** indications: ***RISE & RIDE***—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. ***Protocol S***—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.[2-3]

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).[1]

DME, diabetic macular edema.

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **2.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **3.** Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

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LUCENTIS®
RANIBIZUMAB INJECTION