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PROS AND CONS OF HEADS-UP SURGERY P. 53 • ALTERNATIVE BROW-LIFTING TECHNIQUES P. 56

# REVIEW<sup>®</sup> of Ophthalmology

September 2017

reviewofophthalmology.com

ANNUAL CORNEA ISSUE

## Using Unavailable and Off-label Meds: Getting Tougher?

The lengths physicians will go to in order to save patients' vision. **Page 18**



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- Cross-linking at One Year: How Surgeons Are Using It **P. 23**
  - Work Up Corneal Ulcers Like an Expert **P. 30**
  - How to Diagnose and Manage Conjunctivochalasis **P. 36**

The **FIRST** and **ONLY** NSAID indicated to prevent ocular pain in cataract surgery patients<sup>1</sup>

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FOR YOUR CATARACT SURGERY PATIENTS

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- DuraSite<sup>®</sup> increases ocular surface retention time, resulting in increased bromfenac absorption<sup>2-5</sup>
- Provides 24-hour coverage with BID dosing<sup>1</sup>
- Available in 5 mL bottle

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**BromSITE<sup>®</sup>**  
(bromfenac ophthalmic solution) 0.075%

Formulated with DURASITE<sup>®</sup> DELIVERY SYSTEM

## Indications and Usage

BromSite<sup>®</sup> (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

## Recommended Dosing

One drop of BromSite<sup>®</sup> should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

## Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite<sup>®</sup>, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite<sup>®</sup>. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite<sup>®</sup>, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that BromSite<sup>®</sup> be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- **Keratitis and Corneal Effects:** Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite<sup>®</sup>, and should be closely monitored

for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

- **Contact Lens Wear:** BromSite<sup>®</sup> should not be administered while wearing contact lenses. The preservative in BromSite<sup>®</sup>, benzalkonium chloride, may be absorbed by soft contact lenses.
- **Adverse Reactions:** The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

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

NSAID=nonsteroidal anti-inflammatory drug.

**References:** 1. BromSite<sup>®</sup> [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. 2. Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday<sup>™</sup>) compared with bromfenac in DuraSite<sup>®</sup> 0.075% (BromSite<sup>™</sup>) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. 3. ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. <https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite-vision&rank=1>. Accessed March 2, 2017. 4. Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66. 5. Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139.

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# BromSite® (bromfenac ophthalmic solution) 0.075% Brief Summary

## INDICATIONS AND USAGE

BromSite® (bromfenac ophthalmic solution) 0.075% is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

## CONTRAINDICATIONS

None

## WARNINGS AND PRECAUTIONS

### Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite® (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

### Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

### Increased Bleeding Time of Ocular Tissue

With some NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

### Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

### Contact Lens Wear

BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.

## ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the Brief Summary:

- Slow or Delayed Healing
- Potential for Cross-Sensitivity
- Increased Bleeding Time of Ocular Tissue
- Keratitis and Corneal Reactions
- Contact Lens Wear

### Clinical Trial Experience

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

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Risk Summary

There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

#### Clinical Considerations

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite® during late pregnancy should be avoided.

#### Data

##### Animal Data

Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m<sup>2</sup> basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m<sup>2</sup> basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Lactation

There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

### Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 years have not been established.

### Geriatric Use

There is no evidence that the efficacy or safety profiles for BromSite® differ in patients 65 years of age and older compared to younger adult patients.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m<sup>2</sup> basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m<sup>2</sup> basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m<sup>2</sup> basis).

### Rx Only

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# International Workshop Redefines Dry Eye

**The Tear Film and Ocular Surface Society** recently published the report of the International Dry Eye Workshop II, better known as TFOS DEWS II. One hundred and fifty dry-eye experts from 23 countries met in 12 different subcommittees to create their new report on dry-eye disease. The report is intended to accomplish three things: update the definition, classification and diagnosis of the disease; assess the etiology, mechanism, distribution and impact of the disease; and address its management and therapy. (*For more on the latter topic, see next month's dry-eye-focused issue of Review.*)

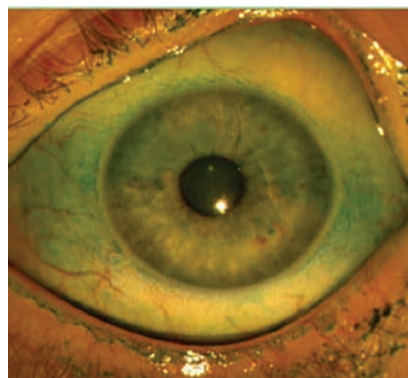
The definition of dry eye proffered in 1995 by the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye<sup>1</sup> stated: "Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort." The first TFOS DEWS report<sup>2</sup> updated the definition by—among other things—calling it a disease with multiple underlying causes: "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."

The new definition generated by DEWS II clarifies this even further

and incorporates new perspectives supported by recent research: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."<sup>3</sup>

J. Daniel Nelson, MD, FACS, chair of the DEWS II report, professor of ophthalmology at the University of Minnesota and an ophthalmologist in the HealthPartners Medical Group in St. Paul, explains how the new definition differs from previous definitions—and why it matters.

"All of the definitions of dry-eye disease have been based on the current literature and knowledge at the time," he says. "The definition suggested by the NIE/Industry workshop defined dry eye as a disorder; in the first DEWS report it was defined as a disease. That's a key difference.



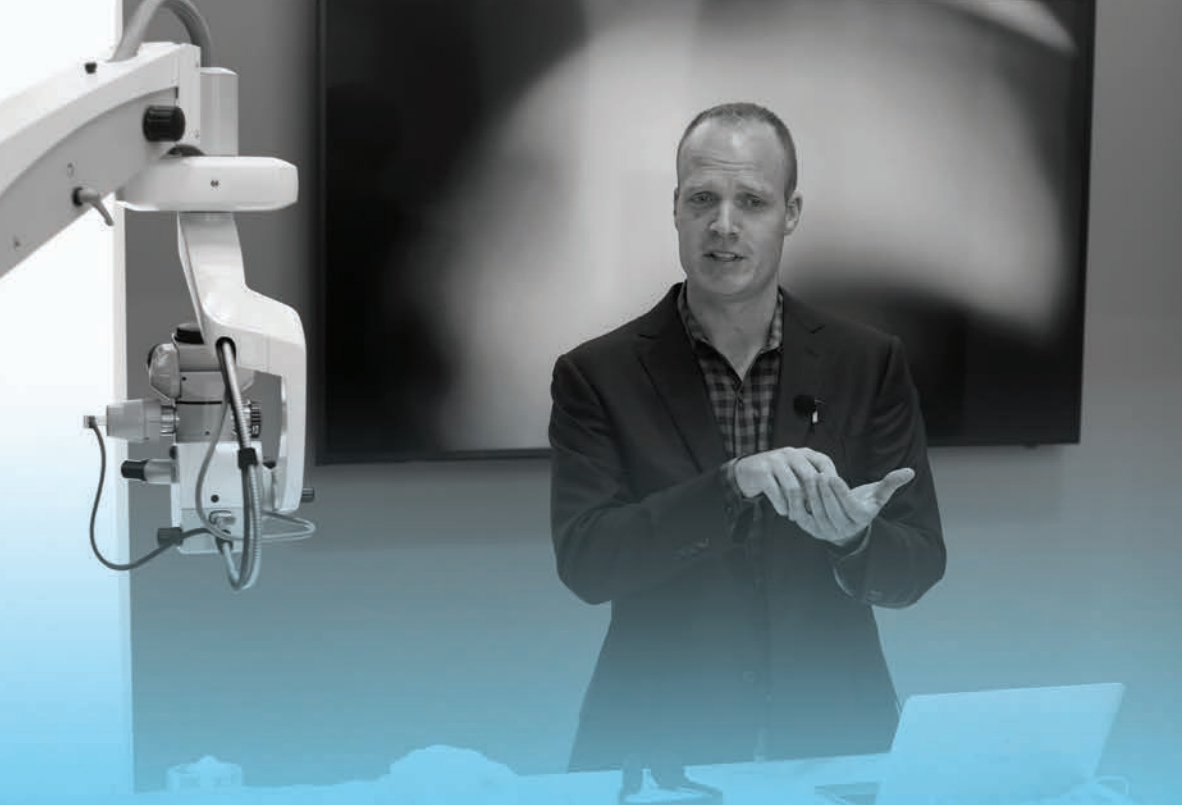
One of the key concepts in the DEWS II definition of dry eye is homeostasis.

The latter also mentioned that tear film osmolarity and inflammation were involved in the disease. However, the way they might be involved in the etiology of dry eye wasn't yet fully fleshed out, which led to a lot of consternation and debate about the inclusion of osmolarity and inflammation in the definition."

Dr. Nelson says a key choice of wording in the latest definition was the word "homeostasis." "Homeostasis of the tear film refers to the process of keeping the tear film condition normal, so that it's able to carry out its normal function—protecting the ocular surface and providing a stable optical interface," he explains. "Any disturbance or loss of tear film homeostasis can cause symptoms and can lead to, or be due to, tear film instability, hyperosmolarity, ocular surface inflammation and damage, as well as neurosensory abnormalities.

"One reason for using a word like homeostasis is that it keeps the definition from being too narrow," he continues. "We used to think that the tear film was made up of three layers. Today we know it's a two-phase tear film with a lipid phase overlying an aqueous-mucin phase composed of a thousand different proteins. If we define DED too specifically, we limit what DED is. If we define it too broadly, then anything could be DED. By defining the disease in terms of a loss of the normal state—homeostasis—the definition avoids those pitfalls. It sets the basis for further research to really define what it

Eric Donnemfeld MD



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is that keeps the tear film in a homeostatic state.”

Dr. Nelson says another key change in the new definition is the mention of neurosensory abnormalities. “One of the issues over the years has been that symptoms often do not correlate with signs,” he says. “A patient may have symptoms, but everything you can measure appears to be normal. That raises the issue of neurosensory abnormalities, which can lead to neuropathic pain. We felt it was important to include that in the definition of the disease.”

Why is a more accurate definition important? Dr. Nelson says one reason is that it affects the ability of clinical trials to provide statistical evidence of a dry-eye product’s efficacy. “We now have two approved drugs for treating dry eye, but many have failed to get approval,” he notes. “One of the main reasons so many have failed is that the definition of dry eye used to select patients for the studies was very broad-based. When you take a group of heterogeneous patients and put them in a study, you’re going to get heterogeneous results. This new definition and classification allows us to be very specific about what we’re testing. We can look for evidence of loss of tear film homeostasis, with specific variables that might include osmolarity, corneal and conjunctival staining and tear film instability. In the past, it was very easy to lump all dry-eye patients together.”

Dr. Nelson says he believes the new definition will help clinicians as well. “A good definition will help you decide whether a patient really does have DED, and that’s going to help determine what treatments you pursue,” he says. “I see many patients who’ve been to two or three different doctors; they come in because they’re not responding to treatment. That’s because right now, most clinicians are basing their diagnosis on

symptoms. The new definition says that dry eye is all about the loss of tear film homeostasis. It’s about signs as well as symptoms. If you read the pathophysiology section of the DEWS II report, it talks about the ‘vicious circle.’ This refers to the idea that all four signs—tear film instability, hyperosmolarity, ocular surface inflammation/damage, and neurosensory abnormalities—are like a circle. Any point on that circle can be the starting point and eventually lead to dry-eye disease. So as a clinician diagnosing the problem, you should be looking for signs of hyperosmolarity or inflammation, ocular surface damage, and potentially neurosensory abnormalities. Hopefully the new definition will encourage clinicians to look beyond symptoms.”

1. Lemp MA. Report of the national eye institute/industry workshop on clinical trials in dry eyes. *CLAO J* 1995;21:4:221e32.
2. The definition and classification of dry eye disease: Report of the definition and classification subcommittee of the international Dry Eye Workshop. *Ocul Surf* 2007;5:2:75-92.
3. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocular Surf* 2017;15:3:276-83.

## Fovista Fails Phase III

**Pharmaceutical company Ophthotech announced** that the prespecified primary endpoint of mean change in visual acuity at 12 months was not achieved in its Phase III clinical trial undertaken to investigate the potential superiority of Fovista (pegpleranib) anti-platelet-derived growth factor therapy in combination with Eylea (aflibercept) or Avastin (bevacizumab) anti-VEGF therapy, compared with Eylea or Avastin monotherapy for the treatment of wet age-related macular degeneration. The addition of 1.5 mg of Fovista to an Eylea or Avastin regimen didn’t result in benefit, as measured by the mean change in visual acuity at 12 months. **REVIEW**



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\* Clinicaltrials.gov Identifier: NCT03183089. Publication Pending

† Euromonitor International Limited: Consumer Health Eye Care definition, retail value share, 2016 data

## 12 HRS

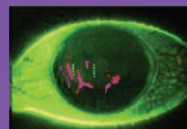
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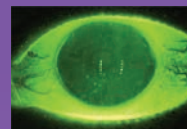
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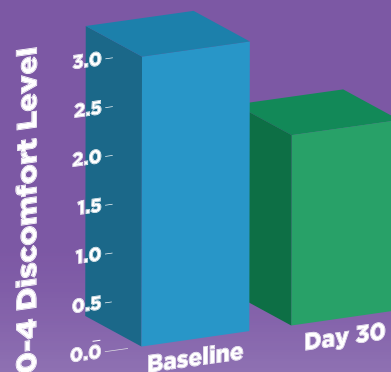


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# BEAR IN MIND THE FORMULATION OF **LOTEMAX<sup>®</sup> GEL**

- **ENGINEERED TO ADHERE TO THE OCULAR SURFACE<sup>1,2</sup>**
  - Adaptive viscosity: Gel at rest, viscous liquid on the eye
  - Drug-related blurred vision was rarely reported (0.25%, 2/813)
- **~70% LESS PRESERVATIVE than LOTE<sup>®</sup> MAX<sup>®</sup> SUSPENSION (loteprednol etabonate ophthalmic suspension) 0.5%<sup>2,3,5</sup>**
- **DOSE UNIFORMITY—EVERY DROP, EVERY TIME**
  - No shaking required to resuspend drug<sup>2,4</sup>
- **pH OF 6.5 CLOSE TO THAT OF HUMAN TEARS<sup>2</sup>**
- **CONTAINS 2 KNOWN MOISTURIZERS<sup>3</sup>**
  - Glycerin and propylene glycol

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## Indication

LOTEMAX<sup>®</sup> GEL (loteprednol etabonate ophthalmic gel) 0.5% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

## Important Safety Information about LOTE<sup>®</sup> MAX<sup>®</sup> GEL

- LOTE<sup>®</sup> MAX<sup>®</sup> GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, and where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Patients should not wear contact lenses when using LOTE<sup>®</sup> MAX<sup>®</sup> GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

Please see brief summary of Prescribing Information on adjacent page.

References: 1. Rajpal RK, Fong R, Comstock TL. Loteprednol etabonate ophthalmic gel 0.5% following cataract surgery: integrated analysis of two clinical studies. *Adv Ther*. 2013;30:907-923. 2. Coffey MJ, Decory HH, Lane SS. Development of non-settling gel formulation of 0.5% loteprednol etabonate for anti-inflammatory use as an ophthalmic drop. *Clin Ophthalmol*. 2013;7:299-312. 3. LOTE<sup>®</sup> MAX<sup>®</sup> GEL [package insert]. Tampa, FL: Bausch & Lomb Incorporated. 4. Apt L, Henrick A, Silverman LM. Patient compliance with use of topical ophthalmic corticosteroid suspensions. *Am J Ophthalmol*. 1979;87(2):210-214. 5. LOTE<sup>®</sup> MAX<sup>®</sup> SUSPENSION [package insert]. Tampa, FL: Bausch & Lomb Incorporated.

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loteprednol etabonate  
ophthalmic gel 0.5%

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Visit [www.LOTEMAXGEL.com](http://www.LOTEMAXGEL.com)

## BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Lotemax Gel safely and effectively. See full prescribing information for Lotemax Gel.

# Lotemax (loteprednol etabonate ophthalmic gel) 0.5%

Rx only

Initial Rx Approval: 1998

## INDICATIONS AND USAGE

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

## DOSAGE AND ADMINISTRATION

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

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

## CONTRAINDICATIONS

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

## WARNINGS AND PRECAUTIONS

### Intraocular Pressure (IOP) Increase

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

### Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

### Delayed Healing

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

### Bacterial Infections

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

### Viral Infections

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

### Fungal Infections

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

### Contact Lens Wear

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

## ADVERSE REACTIONS

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

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

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Teratogenic Effects

Loteprednol etabonate has been shown to be embryotoxic (delayed

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

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

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

### Nursing Mothers

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

### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### Geriatric Use

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

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment Of Fertility

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

## PATIENT COUNSELING INFORMATION

### Administration

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

### Risk of Contamination

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

### Contact Lens Wear

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

### Risk of Secondary Infection

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

Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC  
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US Patent No. 5,800,807

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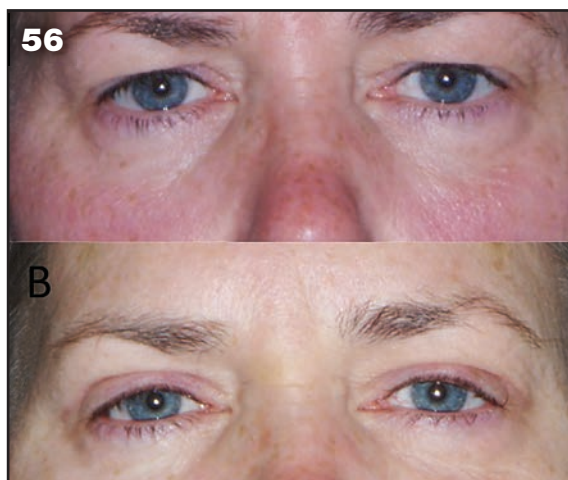
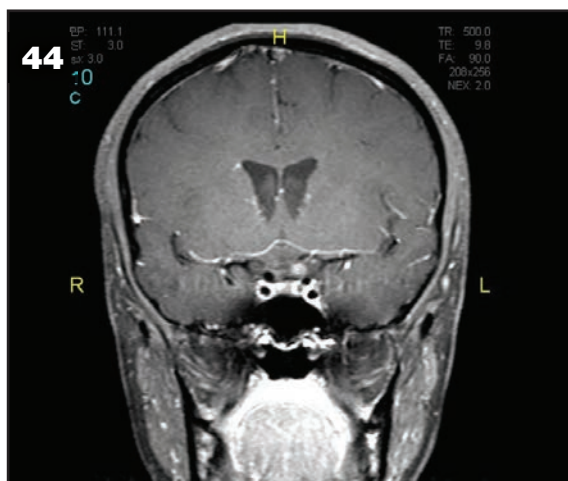
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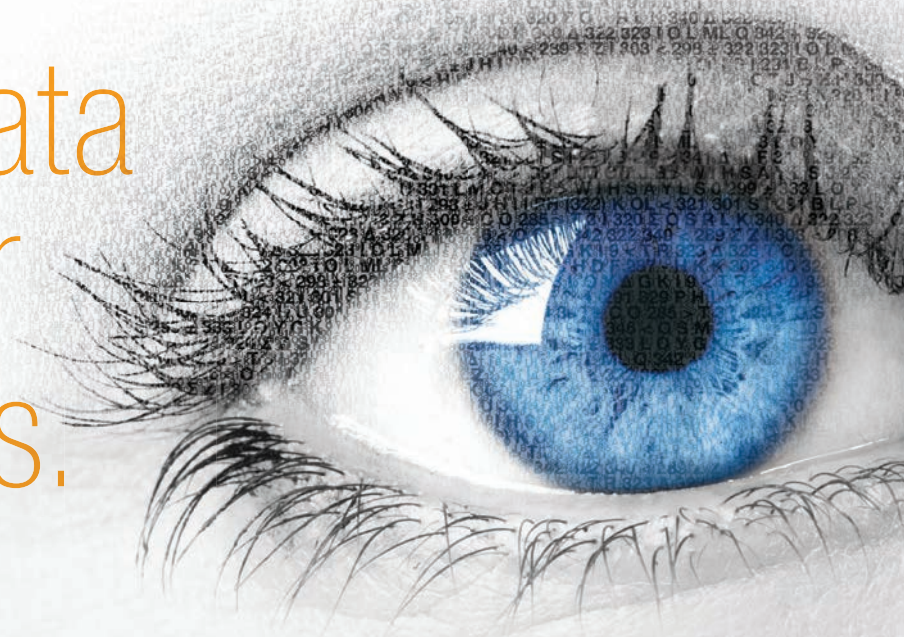
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# Getting Drops Onto the Eye: Low-tech Solutions

There's more than one way to help your patients put their medications where they belong.

*Christopher Kent, Senior Editor*

**T**oday, the struggle to increase patient compliance with medication use is becoming increasingly high-tech. New options often focus on taking the patient out of the equation by enabling extended delivery of a drug. Devices potentially making this possible range from intravitreal implants to punctal plugs to rings that sit in the conjunctival fornix and slowly release medication.

Nevertheless, placing drops on the eye is still the method of delivery almost every patient uses, and that old-school technology is likely to remain in use for the foreseeable future. That brings us back to a basic, well-known problem: Many patients have difficulty using eye drops properly.

Faced with a dismal rate of accurate drop use among patients, most doctors focus on trying to teach patients better eye drop application technique or try to get someone else to help the patient instill the drops. However, there are some clever, readily available low-tech eye drop application devices that may do a lot to help your patients succeed in getting their drops onto their eyes. These devices fall primarily into three categories: those

that attempt to position the bottle over the eye in a consistent manner while holding the eyelids open; those that use surface tension to deliver a drop onto the eye via an intermediary device; and one or two that offer unique approaches to getting the drops onto the eye. Here, we'll provide a review of some of the products in each category.

## Bottle Managers

The first category is the simplest: The eye dropper bottle is snapped into, or otherwise encased in, a plastic device that acts to hold open the eyelids and positions the dropper tip above the eye when the head is tilted back. Unfortunately, this type of design has some obvious shortcomings

(and tends to get mixed reviews from users). The advantages include that it keeps the bottle tip from touching the eye and holds the eyelids out of the way while the drop is being applied. The most obvious problems are that the patient still has to tilt his head back, and there's no guarantee that the drop will land on the eye. Furthermore, the patient may squeeze out multiple drops by mistake.

Products in this category (*see pictures, below*) include:

- **AutoDrop Eye Drop Guide.** The tip of the dropper bottle clips into the lid of this guide, which the manufacturer says was developed in collaboration with the British Royal National Institute for the Blind. The guide, which holds the eye open with the bottle positioned over the eye,

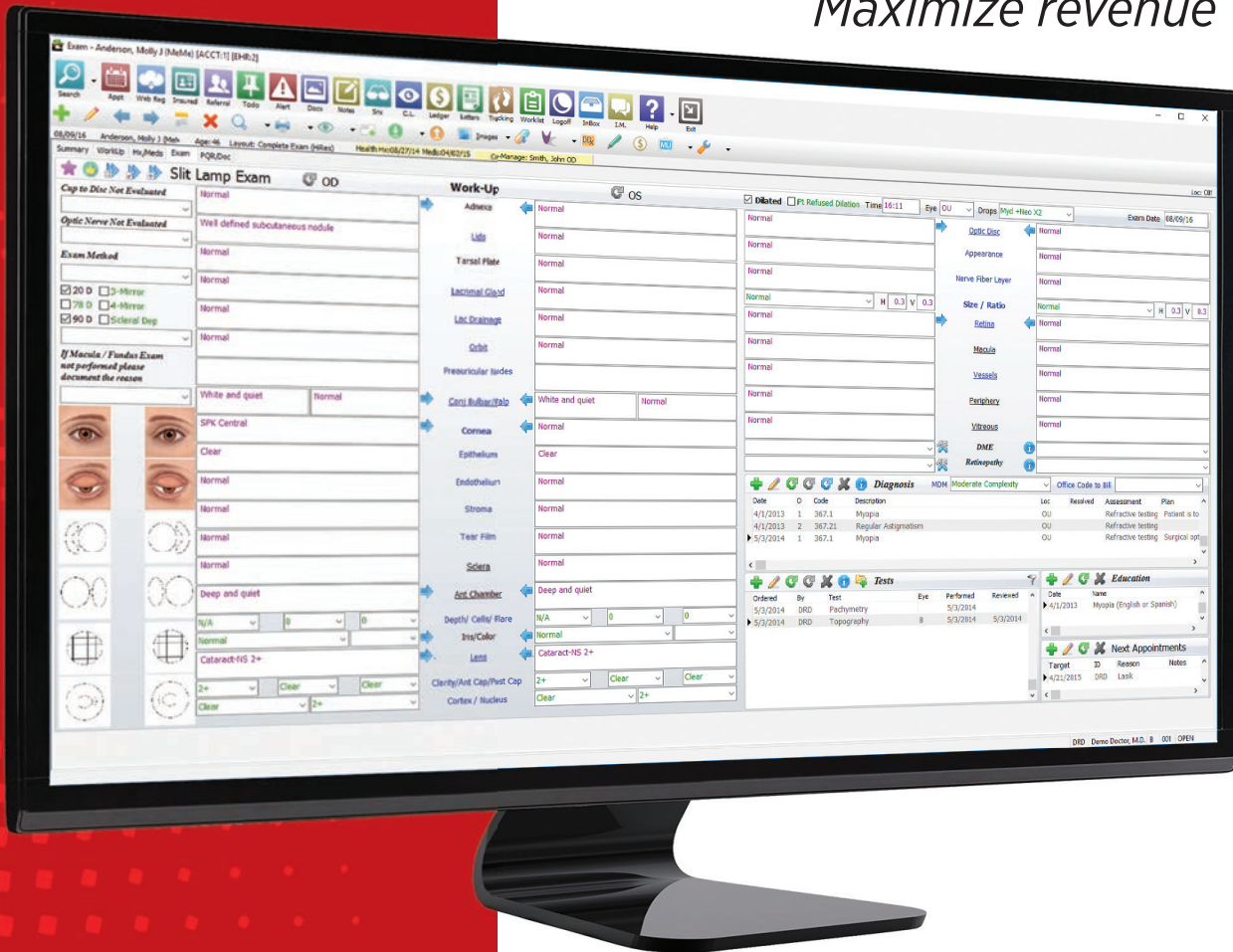


Some products claim to help position the bottle over the eye and make it easier to squeeze.



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Several products use capillary action to make the drop “jump” from the device onto the eye.

has a pinhole that lets light in; according to the manufacturer, when the patient looks at the pinhole, the eye is correctly positioned to receive the drop. This device can be used in conjunction with AutoSqueeze, another plastic device that goes around the bottle itself (rather than clipping onto the tip); it uses the lever principle to make it easier to squeeze the bottle. You can find more information about both items at: [maddak.com/autodrop-eye-drop-guide-p-28115.html](http://maddak.com/autodrop-eye-drop-guide-p-28115.html).

- **Flents Ezy Drop Guide & Eye Wash Cup.** This plastic bottle holder resembles an eye-wash cup, and the manufacturer claims it can be used for that purpose as well. You can check it out at [amazon.com/Flents-Drop-Guide-0-058-Pound/dp/B0011YK3NS](http://amazon.com/Flents-Drop-Guide-0-058-Pound/dp/B0011YK3NS).

- **Opticare Eye Drop Dispenser.** In addition to positioning the bottle over the eye, this device is designed to make it easier for the patient to squeeze the bottle. The manufacturer claims that it essentially makes a small bottle as easy to manage as a larger bottle. For more information, visit [goldenophthalmics.com/products/index.php/opticare-eye-drop-dispenser.html](http://goldenophthalmics.com/products/index.php/opticare-eye-drop-dispenser.html).

### Using Capillary Action

A less intuitive but more interesting approach to getting drops onto the eye involves placing a single drop into a holder and then bringing the holder close to the eye, allowing the drop to “jump” onto the eye from the device.

This approach has several advantages, including increasing the likelihood that only one drop will actually be used at a time; eliminating the need for the patient to tilt her head back; making it next-to-impossible to miss the eye; and keeping the bottle tip away from the eye, thus avoiding contamination. Potential drawbacks include the need to keep the device clean, and possible contacts between the device and the eye. Products using this approach include:

- **Magic Touch: The Eye Drop Helper.** This device, which resembles a small rubber bell about the size of a thimble, is placed on a fingertip; with the finger held vertically, a drop is placed into a small dimple at the tip of the device. The patient then leans forward, and when the device gets close to the eye, the drop “jumps” onto the eye. Designed by Julius Shulman, MD, the Magic Touch device is BPA-free and made of medical-grade silicone. The manufacturer says that antimicrobial silver ions in the material eliminate up to 99.99 percent of microbes, so the device can be kept clean by simply rinsing under warm water after use. You can find more information at [magic-touch-eye.myshopify.com](http://magic-touch-eye.myshopify.com).

- **SimplyTouch.** This device is a small, reusable handheld applicator with a tiny disc at the top, onto which a drop is placed; surface tension keeps the drop in place. One side of the disc has no rim; the other has a rim to help less viscous drops stay on the disc. The patient places a drop onto

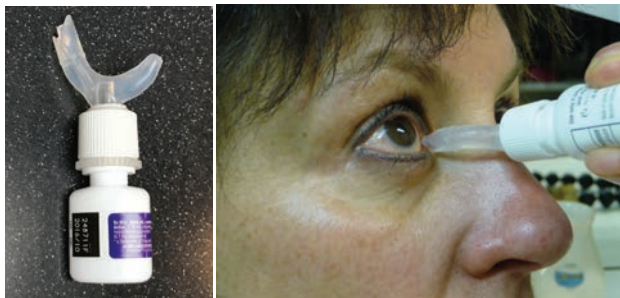
the plastic applicator, pulls down the lower lid while looking in a mirror, brings the tip of the applicator close to the eye, and the drop jumps onto the eye. Advertised features include that the device can be used with or without glasses on, and that the device is easy to clean and store after use. Because it’s easier for the patient to control the drop usage, the manufacturer claims that patients get up to 50 percent more uses per bottle. You can learn more at [simplytouchusa.com](http://simplytouchusa.com).

- **OptiAide.** This device, which looks more high-tech than the others, can hold up to five drops in its five chambers. (In the product photo, each chamber has been filled with different food coloring to make them easier to see.) Unlike the other devices, this one is held in front of the eye, allowing the drop to jump onto the eye, theoretically preventing the device from contacting the cornea. However, it does require moving the eyelids and lashes out of the way. You can find more information at [contactlenskit.com/optiaide/](http://contactlenskit.com/optiaide/).

### A Targeted Approach

One of the most unique dropper-assist designs was created by Jonathan Cress, MD, an ophthalmologist in Santa Cruz, Calif., who’s been in practice for more than 40 years. “The Cress dropper is an arched tube that screws onto the dropper bottle,” he explains. “It references the nose so the tip can be comfortably and steadily placed in the medial canthal area. Once the tip is properly placed, the bottle is squeezed; the drop leaves the aperture, slides down and off the little ramp onto the delivery tip and into the eye. (See photos, facing page.) The patient releases the bottle when she feels the drop. The current version of the dropper has no metering component, but most patients learn to adjust their bottle squeeze to release just one drop.”

# 24<sup>TH</sup> ANNUAL **OPHTHALMIC** *Product Guide*



The Cress Dropper allows a drop to slide into the eye.

Asked about keeping the drops sterile, Dr. Cress notes that the delivery tip is designed to physically isolate the distal aperture from the delivery surface. “The purpose of this design is to prevent conjunctival or skin bacteria from being aspirated back into the bottle, contaminating the drops,” he says. “Cleaning the tip after each use would be ideal, but it’s not necessary. In my experience, the rate of bottle contamination is 25 percent lower than with standard dropper tips that aren’t supposed to be touched. In fact, I’m not aware of any external ocular infections caused by the use of my dropper.”

Dr. Cress says that patients who use the dropper are almost universally happy with it. “I have a substantial population of patients who can’t get drops in their own eyes with a standard dropper,” he says. “Those patients have to have their spouse or someone else instill their drops. With my dropper, most of them can do it themselves. However, some patients who lack manual dexterity or have weak hands still may find it difficult or impossible to meter a drop by squeezing accurately. They still waste drops and occasionally miss, so they’re less happy with it.”

Dr. Cress says he’s observed a difference in outcomes when glaucoma patients switch to his device, although he doesn’t have concrete data to prove it. “I’ve had patients who seemed to be failing at drop therapy, but after using this device, their intraocular pressure stabilizes and their visual field loss ceases,” he says. “To me, this indicates that they weren’t effectively instilling drops before, but with the dropper they are. Additionally, patients using the dropper rarely run out before a refill is due.”

Dr. Cress says he originally created the device for his 9-year-old son who was suffering from dry eye. “Once I had a working model I licensed it to Wilson Ophthalmic, who made about 20,000 of them,” he says. “I’m currently working on improvements to the design. The next version accurately meters a single drop, is easier to squeeze and makes it easier to get the drop into the eye. I’m open to proposals for manufacturing the new model.” For more information about the original version, visit [amazon.com/Cress-Dropper-EyeDrops-Professional-Model/dp/B004R8TOGM](http://amazon.com/Cress-Dropper-EyeDrops-Professional-Model/dp/B004R8TOGM). **REVIEW**

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**REVIEW**  
of Ophthalmology



# Access to Off-label Meds: Getting Tougher

Christopher Kent, Senior Editor

Well-intentioned restrictions on compounded drugs are making timely treatment challenging.

The use of off-label drugs and devices is very common in the day-to-day practice of medicine. In fact, if a surgeon *fails* to prescribe some off-label medications or use some devices in an off-label manner—for example, antibiotics following cataract surgery, mitomycin-C as an adjunct to surgery, adhesives to close wounds, or topical antibiotics to treat infectious corneal ulcers—he or she could actually be at risk of a malpractice lawsuit. One could even argue that if the off-label use of drugs and devices were forbidden, the result would be disastrous for millions of patients.

There's no question that having FDA approval means a drug has been thoroughly tested for safety and efficacy. However, not having approval for a particular drug or device—or a specific use of an approved drug or device—doesn't mean the drug or device isn't safe and effective. That's because the approval process itself comes with numerous real-world caveats, including:

- **Executing the trials necessary to get FDA approval can be very costly.** This makes it difficult or impossible for many smaller manufacturers to get approval for a product.
- **Some treatments are so inexpensive that the high cost of the**

**approval process would never be recouped.** This leaves many highly effective treatments unapproved.

- **Running a clinical trial may not be feasible.** The size or nature of an afflicted population can make a clinical trial logistically impossible.

- **Even when FDA approval is granted, it's very specific and limited.** Approval is based on the nature and outcomes of the clinical trials that led to approval. Because of cost and logistical challenges, an FDA clinical trial can't represent the full spectrum of uses a drug may offer, and the approval will reflect that.

- **The beneficial uses of a drug or device always evolve over time.** If every newly discovered use of a drug or device had to go through an expensive approval process, the practice of medicine might never move forward.

In reality, many treatments that have not gone through the FDA-approval process have been well-demonstrated to be helpful and are widely used; quite a few are even standard of care. Many have been tested in clinical trials reported in the peer-reviewed literature that were not done under FDA supervision. Others that are less amenable to testing in clinical trials have been shown to be safe and effective over the course of many years of use in the real world.

## The Compounding Factor

Compounding drugs into different formats or combinations has been common practice for many years, allowing doctors to address conditions beyond those specifically approved by the FDA. Despite this, obtaining many compounded drugs has recently become far more difficult as a result of the Drug Quality and Security Act. The law was passed by Congress in 2013

following the deaths of 64 individuals in a meningitis outbreak attributed to a drug-compounding pharmacy in New England; the new law gives the FDA increased authority to regulate and monitor the manufacture of compounded drugs.

As it turns out, these well-intended new rules, meant to increase safety, are apparently having an unintended side effect: curtailing the availability of eye-sight-saving medications. The cost of implementing new procedures, such as extensive safety testing, has caused many compounding pharmacies to drastically curtail their offerings. For example, in 2013, prior to the implementation of the DQSA, one pharmacy that's still in operation offered a list of almost 200 compounded drugs and injectables. That list included five anti-allergy preparations; 38 antibiotic preparations; seven antivirals; 10 antifungals; three cytotoxic agents; nine preparations used for diagnosis (e.g. lissamine green); 26 compounds for treating dry eye; 32 preparations for managing glaucoma; and more than 60 other compounded medications. Today, as a result of the DQSA, that pharmacy has converted to a 503B outsourcing facility and offers a total of 10 compounded formulations.

The new rules are also causing other unintended consequences. Among those is a new definition of compounding that impacts some com-



As a result of recent regulations, many compounding pharmacies that once provided scores of compounded drugs now compound fewer than a dozen.

mon, beneficial surgical practices. For example, adding epinephrine to the lidocaine used to numb the eye for cataract surgery is a common surgical practice. It's supported by many peer-reviewed studies, and it demonstrably makes the surgery easier, safer and less costly by keeping the pupil dilated during the course of the surgery. The new guidelines regarding compounding encompass many common practices like this, making these practices a violation of the rules.

Here, three surgeons discuss their experiences obtaining and using off-label medications and how the current situation has affected their practices.

### Going Off-label

Natalie A. Afshari, MD, FACS, Stuart I. Brown MD Chair in Ophthalmology in Memory of Donald P. Shiley; professor of ophthalmology; and chief of cornea & refractive surgery at the Shiley Eye Institute, University of California San Diego, is the chair of the FDA Committee for the American Society of Cataract and Refractive Surgery. Dr. Afshari notes that there are many scenarios in which ophthalmologists use drugs that are off-label or have to be compounded. "These drugs are very important in practice for many ophthalmology subspecialties," she says. "Retina specialists mainly use Avastin and antibiotics;

those of us treating the cornea use antibiotics and anti-amoeba medications; glaucoma specialists use mitomycin-C; and cataract surgeons use intracameral injections of antibiotics.

"An acanthamoeba corneal ulcer can be devastating to vision," she continues. "There's no approved drug for the treatment of acanthamoeba, so we use options such as polyhexa-methylene biguanide—a

pool cleaner that can be diluted—to kill the amoeba. This compounded eye drop should be inexpensive, but over time it's become very costly and is no longer easily accessible. We recently treated a patient with an acanthamoeba corneal ulcer, and unsuccessfully spent two hours calling every compounding pharmacy we knew of to locate these drops. I ended up texting my colleagues around the country to find out where I could find these drops, and we eventually found a pharmacy many hours away that still prepares it. Another option for treating acanthamoebic keratitis is chlorohexidine, but physicians encounter similar difficulties obtaining compounded chlorohexidine."

Dr. Afshari notes that there are other kinds of corneal ulcers that require compounded drugs for treatment as well. "We may treat bacterial ulcers with compounded antibiotics such as vancomycin or tobramycin," she says. "Unfortunately, there are fewer and fewer compounding pharmacies in the U.S., which affects the availability of these medications. Another compounded medicine is topical alpha interferon for the treatment of ocular surface neoplasia. (The alternative for these patients is surgical excision.) Decreasing availability of topical interferon has made it difficult for some patients with ocular surface neoplasia to pursue this less-invasive therapy.

## Antibiotics and Cataract Surgery

One common situation that involves using drugs in a non-approved manner is antibiotic prophylaxis following cataract surgery. David F. Chang, MD, a clinical professor of ophthalmology at the University of California, San Francisco, spoke about this issue at the 2017 meeting of the American Society of Cataract and Refractive Surgery. “I think most of us would consider some form of antibiotic prophylaxis to be standard-of-care for intraocular surgery,” he says. “The fact that there’s no topical or intraocular antibiotic that’s FDA-approved for this purpose raises two separate but related issues.

“First is the off-label use of an antibiotic solution that’s FDA-approved and commercially manufactured for another indication, such as conjunctivitis,” he explains. “We have a wide selection of commercially manufactured topical ophthalmic antibiotics in the United States, but none are FDA-approved for endophthalmitis prophylaxis. Nevertheless, in our 2014 ASCRS survey on endophthalmitis prophylaxis practice patterns,<sup>2</sup> 91 percent of respondents were using perioperative topical antibiotics for infection prophylaxis for cataract surgery. Such prevalent use, however, is all off-label.

“Second,” he continues, “approximately half of the survey respondents were using intraocular antibiotic prophylaxis. Because there’s no commercially available antibiotic solution manufactured for intraocular use in the U.S., many ambulatory surgical centers are using a compounding pharmacy or mixing the antibiotics themselves for intracameral antibiotic prophylaxis. It’s very unfortunate that American patients do not have access to a commercially manufactured antibiotic solution for this indication.”

Dr. Chang acknowledges that injecting an intraocular antibiotic at the end of cataract surgery is not without risk. “When a devas-

tating complication occurs, such as hemorrhagic occlusive retinal vasculitis, risk-management concerns inevitably arise,” he says. “Physicians are allowed to—and regularly do—use drugs for off-label indications. In this situation, off-label status isn’t the main problem per se, but rather: What was the evidence and rationale supporting the drug’s use, and what were the alternatives?”

Dr. Chang notes that some of the rare but potential problems with the intraocular injection of compounded drugs were brought home recently when about 50 patients in Dallas developed acute retinal toxicity following intravitreal injection of a moxifloxacin-triamcinolone mixture provided by a local 503A compounding pharmacy. “Injecting an antibiotic-steroid mixture into the vitreous to replace the need for topical therapy following routine cataract surgery is a relatively new practice, and there are two potential lessons here,” he says. “First, because the eye is so sensitive to even minute amounts of toxic impurities, I personally prefer to use a 503B outsourcing facility for any compounded drugs that will be injected into the eye. Compared to a 503A compounding pharmacy, 503B facilities must pass more stringent requirements to gain this FDA designation.

“Second,” he says, “a toxic substance inadvertently entering the anterior chamber may cause toxic anterior segment syndrome, or TASS, but severe endothelial toxicity can ultimately be treated with an endothelial keratoplasty. In contrast, a toxic substance reaching the posterior segment may cause retinal toxicity with permanent loss of vision. Although the risk of toxic posterior segment syndrome is small, cataract surgeons must consider this when balancing the need for an intravitreal injection of a compounded drug.”

—CK

Similarly, tacrolimus is a compounded medicine that is used to address recalcitrant atopy in patients with allergic eye disease. Although it’s still available in the United States, tacrolimus has become increasingly difficult to find. We’ve called many different pharmacies before finding one that prepares tacrolimus.”

It’s important to note that while some of the nonapproved treatments involve drugs that were approved for other medical purposes, some drugs haven’t been approved by the FDA at all. “There is a difference,” says Dr. Afshari. “For example, the diluted pool cleaner we use to treat *Acantham-*

*oeba*, polyhexamethylene biguanide, isn’t approved. What company would spend millions of dollars to get approval for a pool cleaner? It wouldn’t make economic sense for them to do that. Nevertheless, for years it’s been the practice to use this chemical for treatment of *Acanthamoeba*. We even published a paper showing that it works in *Aspergillus* keratitis.<sup>1</sup> It hasn’t been approved, so it’s considered off-label. But it is standard of care.”

### Compounding Onsite

One side effect of the cutback in available compounded medications is

that practices have been forced to do more drug compounding on their own in order to save some patients from vision loss or blindness.

Richard Duffey, MD, a corneal specialist in Mobile, Ala., who also teaches at the University of South Alabama, notes that recent regulations have made it extremely expensive for pharmacies to continue offering these services. “In addition to the cost of the equipment, the rare cases in which something has gone wrong have raised the cost of insurance to the point at which pharmacies can’t cover their costs,” he says. “This became an issue of liability in Alabama, so our sources

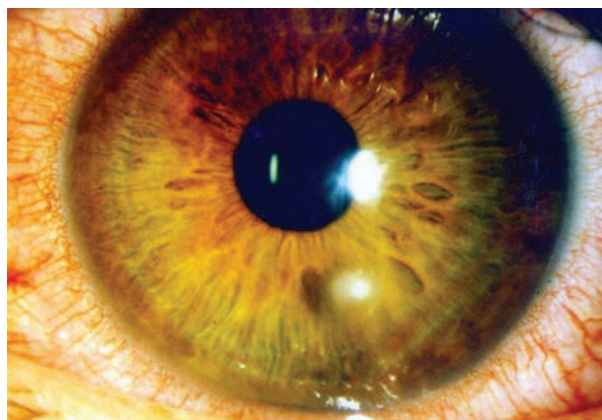


stopped compounding sterile eye drops for us. Now we have to go out of state to find a place that has these commercially available, with the delay that entails. In some cases, the compounded drops are not available anymore, anywhere. Then we have to make them up ourselves.”

Dr. Duffey says his practice has to create drops for patients at least a couple of times a month—more than 25 times a year. “If you’re a corneal specialist, I don’t see how you can treat people without having to go outside of the box,” he says. “Sometimes we have to treat a problem the way we treated it in the past, despite the fact that we can’t get pharmacies to compound these medications locally. We need them to be readily available. The alternative is letting the patient lose an eye.”

Dr. Duffey says a similar problem arises with antifungals. “We often treat local peanut farmers who spray antifungals onto their peanut crops,” he explains. “They can get a black fungus called *Aspergillus* that’s very resistant to treatment. One young patient had a very deep and extensive corneal ulcer that turned out to be *Aspergillus*. He needed to be treated with a fortified antifungal that’s not commercially available. In a situation like this we take a readily available IV medication and use dilution to convert it into a sterile eye drop. Sometimes we have to do this to be able to treat patients with fortified antibiotics or antifungals in a timely manner.

“In the case of this patient, we used this method to make up a fortified antifungal solution at a concentration that allowed us to inject it directly into his cornea to treat the infection,” he continues. “We also created sterile eye drops for the patient to use. This patient ended up with a very good result after several months of treatment,



John Sheppard, MD

Corneal problems such as ulcers frequently require treatment with compounded medications; lack of timely availability may put the eye at risk.

although the infection recurred about three weeks after discontinuing the medication. We had to go through a second round of treatment before we completely eradicated it, which is not unusual with a fungal infection. They tend to be deep and hard to eradicate even after treating for several months.”

Dr. Duffey notes that some medications are FDA-approved to treat infections—just not specifically in the eye. “The guidelines don’t necessarily make a distinction as to where that infection is,” he says. “In this case, the problem was to get it into an eye-drop form, because an IV medication is no help when a patient has a deep corneal ulcer. We need to be able to put the medication where the fungal infection is via an injection into the cornea or a sterile eye drop.”

Dr. Duffey mentions another treatment that his practice has to create in-house: acetylcysteine eye drops. “A number of my patients use the acetylcysteine drops we make up,” he says. “The drops are made by diluting the product Mucomyst, which is prescribed to break up pulmonary secretions—thick mucous in the lungs. Pulmonary doctors often prescribe this drug in a nebulizer, allowing the patient to breathe it in. Patients with severe dry eye often develop filamen-

tary keratitis, mucous filaments on the cornea; this medication, when diluted, does a fabulous job of dissolving those filaments. That makes it a very important medication from a patient comfort and visual acuity standpoint, especially for someone who gets these filaments recurrently. Acetylcysteine is not commercially available as an eye drop, so we simply make up the drops in the office.

“When we have to create drops in our practice, we use sterile technique in a specially cleaned space under sterile conditions, and to my knowledge, we’ve never caused a problem in any patient,” Dr. Duffey adds. “On the other hand, if we don’t make up these medications, some of our patients are going to lose an eye to an infection.”

Dr. Duffey acknowledges that compounding a drug in-practice does mean accepting liability if something goes wrong. “Is it worth taking on the liability when an eye will be significantly damaged without this treatment? In my opinion it is,” he says. “I’ve been in practice almost 30 years since my fellowship, and many of these are treatments we routinely used 30 years ago. I can’t conceive of going backwards in medicine. Would I rather take on some increased liability or watch some of my patients lose an eye, knowing that five years ago I could have treated their problem? You do what you need to do to save your patients’ vision.”

## Speed of Access

Dr. Afshari points out that being able to obtain a medicine within a few hours is often a big issue. “Compounding pharmacies are good about getting the drug to you or the patient quickly,” she says. “Once we order it, they’ll FedEx it overnight so the patient gets

it by the next day. However, in the case of an infection, it's preferable to not wait even that long, because many infections progress significantly in 24 hours. In some situations it would be helpful if in-house pharmacists could make up small quantities of a drug such as vancomycin or tobramycin for the patient, to avoid delaying time-sensitive treatment."

Dr. Duffey says he frequently needs to treat local patients with fortified antibiotics or antifungals that are not readily available. "Central corneal ulcers that are bacterial in nature need treatment with fortified antibiotics," he points out. "Traditionally, pharmacies would compound them for us, but today, at least here in Alabama, it's almost impossible to find a compounding pharmacy that will make sterile eye drops. And it's very hard to get them in a timely fashion when you have to order them from out of state, which can involve a 24- to 48-hour delay."

Some highly beneficial drugs are not even sold in the United States, although they may be easily obtained outside the country. "I sometimes have drugs mailed to me by pharmacies in Australia," says Dr. Duffey. "A drug like Brolene [propamidine isetionate], an antiparasitic for *Acanthamoeba* infections, is available at local apothecary or pharmacy shops in England for the equivalent of about \$10 or \$12. So, whenever I go to England I buy half a dozen bottles, bring them back and keep them in my refrigerator. I use them whenever I need to treat an *Acanthamoeba* infection, as a supplement to other stronger pharmacy-formulated medications that are available outside the state. Luckily, *Acanthamoeba* is slow-growing, so the patient won't be seriously harmed if obtaining the treatment takes several days."

Dr. Afshari occasionally treats acanthamoebic keratitis with Brolene as well. "Sometimes our patients find

out about this medication online and obtain Brolene on their own from the United Kingdom, and then send it to themselves via a family member," she says.

*"In many practices, it used to be that if you needed serum tears, you'd simply draw the blood and send a technician to centrifuge it and dilute it down. Physicians did this because it would allow them to provide the tears to the patient right away."*

— Natalie Afshari, MD

Dr. Afshari says that serum tears are another treatment that's becoming more and more difficult to obtain. "These tears are created from the patient's blood," she explains. "They can be very helpful for healing persistent corneal epithelial defects, but fewer and fewer pharmacies are making them. Our practice is in California, but we now have to send a patient's blood to Kansas to get the serum tears made, which delays treatment and increases cost."

"In many practices, it used to be that if you needed serum tears you'd simply draw the blood and send a technician to centrifuge it and dilute it down," Dr. Afshari continues. "Physicians did this because it would allow them to provide the tears to the patient right away. Eventually, however,

they stopped doing it themselves because of regulations. Similarly, fortified vancomycin and tobramycin are still available through compounding pharmacies, but I know of practices that were making their own vancomycin drops and giving them to the patient, because patients were unable to afford it otherwise."

## Expertise Counts

As noted, there's always some risk associated with using drugs in an off-label manner, but Dr. Duffey points out that a doctor is less likely to run into trouble using off-label options if it's clear that the alternatives have been exhausted. "As a corneal specialist, it's pretty easy for me to justify making up these formulations because I know I've exhausted all the other options," he says. "If you're not a corneal specialist, people could say, 'Why didn't you go to a corneal specialist or a fellowship-trained person who was absolutely sure of the diagnosis and treatment alternatives?'"

"If you're not an authority in the area in question, I'd advise finding a good specialist and deferring to his or her judgment about what the treatment options are," he concludes. "When your patient's treatment needs fall outside of what you can treat with the medications that are available, hopefully that doctor will know of other alternatives." **REVIEW**

*Drs. Chang, Afshari and Duffey have no financial interest in any subject or product mentioned. For more information regarding the pharmacies they use, you can contact Dr. Duffey at richardduffey@gmail.com, or Dr. Afshari at naafshari@ucsd.edu.*

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# Is Cross-linking at a Crossroads?

*Kristine Brennan, Senior Associate Editor*

A look at the potentially life-changing procedure, one year after the first FDA-approved system became available.

**F**DA-approved corneal collagen cross-linking is barely a year old. The Avedro KXL UV system, along with Photrexa and Photrexa Viscous, is approved for patients aged 14 and up with progressive keratoconus or post-surgical ectasia. After years of commercial use abroad, this long-awaited therapeutic option has the potential to halt vision loss for many patients in the United States. In this article, corneal experts discuss the impact that cross-linking has had on their practices, as well as how they combine cross-linking with other procedures.

Outside of the United States, corneal collagen cross-linking has demonstrated long-term ability to stabilize progressive keratoconus and help spare patients the need for corneal transplants.<sup>1</sup> The pivotal Phase III study data<sup>2</sup> that supported the

FDA approval of the Avedro KXL system and the two Photrexas for progressive keratoconus looked at 205 patients at multiple U.S. centers with documented progressive keratoconus, who were randomized into treatment (epi-off cross-linking with Photrexa Viscous and Photrexa riboflavin topical drops and exposure to 3mW/cm<sup>2</sup> UVA light) and sham control (transepithelial Photrexa Viscous and Photrexa without UVA light) groups. KMax at one year decreased from pre-treatment by an average of 1.6 ±4.2 D in the treatment group; it increased by 1 ±5.1 D in the control group. The cross-linked eyes also made gains in CDVA that outstripped those made by sham-control eyes. Corneal haze was the most frequently reported adverse event, and endothelial cell counts had not significantly changed at one year post treatment.

After earning FDA approval for progressive keratoconus in April 2016,

Proper alignment of the UV light source is key to success with the KXL system, which requires a corneal thickness of at least 400 μm after removing the epithelium and before irradiance.

Peter S. Hersh, MD



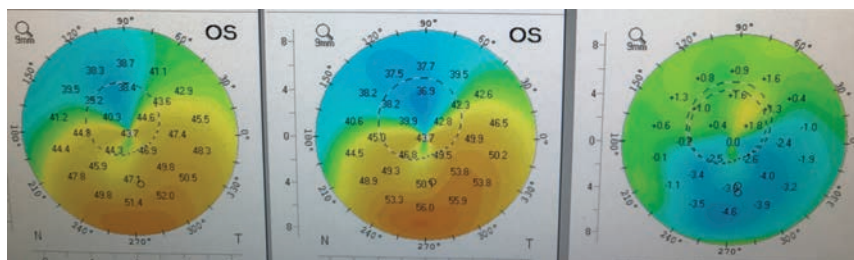


the Avedro cross-linking system was approved for corneal ectasia after refractive surgery in July 2016. The pivotal Phase III study<sup>3</sup> for that indication randomized 179 patients with documented corneal ectasia post refractive surgery into treatment and sham groups: The treatment group underwent epi-off cross-linking; the sham group got riboflavin without removal of the epithelium or UVA irradiance. In the treatment group, mean KMax decreased by  $0.7 \pm 2.1$  D from pre-treatment to one year; mean KMax increased in the sham group by  $0.6 \pm 2.1$  D. The CDVA of the treatment group improved by five letters between preop and 12 months, versus a loss of 0.3 letters for the control group during the same interval. As in the pivotal keratoconus study, corneal haze was the most frequently reported adverse finding.

### Many Protocols in the Mix

“Cross-linking really changes things, because I would see many more transplants in many more people prior to its introduction,” says Yaron S. Rabinowitz, MD, director of ophthalmology research at Cedars-Sinai Medical Center and clinical professor of ophthalmology at UCLA School of Medicine. “It works so well that a large majority of patients that would have needed a transplant can avoid it because they are not progressing. When the disease is detected in the very young, they progress very rapidly; as such, in those patients, progression is now being retarded with cross-linking,” he explains.

Dr. Rabinowitz is an advocate of the Dresden protocol. He has used a UVA delivery device made by Peschke (Waldshut-Tiengen, Germany) under an IDE from the FDA before and since FDA approval of the Avedro KXL system. Dr. Rabinowitz has been involved in a study comparing



Pandy J Epstein, MD

Sagittal difference map showing improved corneal topography of the left eye (far right) after epi-on cross-linking with the CXLUSA photosensitizing agent and UVA light source.

cross-linking alone to a combination of cross-linking and INTACs. Patients continue to be enrolled in this ongoing study, which has been conducted for eight years, with another two years remaining to complete enrollment and analysis of data.

Since the FDA approval of the Avedro KXL system and the Photorexa drugs, colleagues at Dr. Rabinowitz’s surgery center now use the Avedro system per the Dresden protocol. Dr. Rabinowitz uses a slight modification of that protocol, which he believes yields better visual outcomes. He uses a VISX laser in PTK mode to remove the epithelium in his cross-linking patients. “When you remove it with a laser, you smooth the center of the cornea, and that actually improves vision as well as removing the epithelium,” he notes. Dr. Rabinowitz plans to present data from his studies at the upcoming 2017 American Academy of Ophthalmology meeting in New Orleans.

Peter S. Hersh, MD, FACS, of the Cornea and Laser Eye Institute - Hersh Vision Group, professor of clinical ophthalmology and director of cornea and refractive surgery at Rutgers Medical School and a visiting research collaborator at Princeton University, was the medical monitor for the clinical trials of the KXL system. “We did our first case back in 2008 in the original clinical trials,” he says. He thinks that KXL’s classic Dresden protocol-based method of cross-linking is the best starting point for doctors interested in offering the

procedure. “Now we have an FDA-approved procedure, and it’s important to note that to date, in the worldwide literature, there isn’t anything that’s shown better results,” he says. “So starting out, I certainly think practitioners should use this well-studied and proven protocol while additional clinical trials continue to advance the field.” Dr. Hersh, who is also involved in investigating an epi-on protocol, adds, “Certainly, it’s not going to remain this way forever; there are going to be improvements and changes. But it is a good starting point.”

Brad H. Feldman, MD, an instructor at the Wills Eye Hospital and in practice at Philadelphia Eye Associates, says that since initially offering cross-linking in the spring of 2016, his practice has undergone some major changes. “It has allowed me to finally treat patients in the region who had been losing vision from keratoconus but had no access to this proven treatment to halt disease progression and potentially improve vision,” he says.

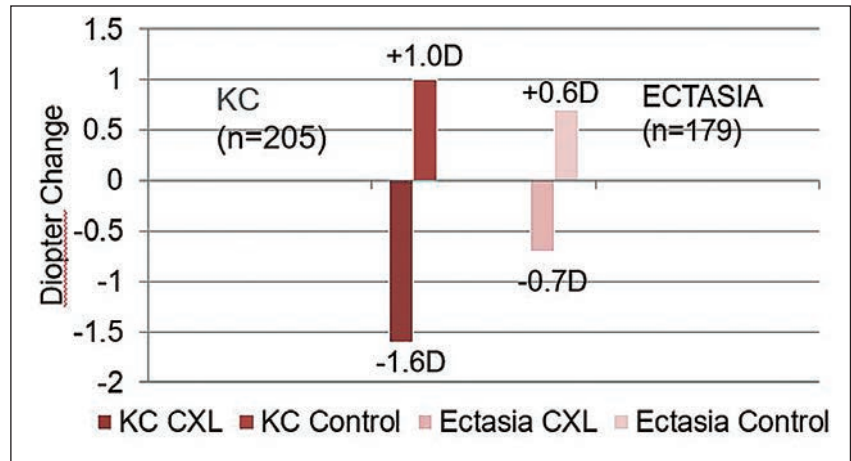
“I have had to build in time for lengthy pre-treatment evaluations and discussions about this new treatment,” Dr. Feldman continues. “Many patients have either never heard of the treatment or have misunderstandings about corneal collagen cross-linking. We have also had to change my office schedule to make room for the treatment session, which we perform in the office during a clinic day rather than in the

operating room on a separate day. I generally treat on Mondays or Tuesdays, see them postoperative day one, and then remove the bandage contact lens on Friday or Saturday.”

Sometimes, however, things are less than straightforward. “Often, patients have asymmetric disease. This may mean that one eye is going to be monitored for progression rather than treated, or one eye may be too advanced and need keratoplasty,” he explains. Dr. Feldman has also experienced the effect of CXL referrals from other providers, and an increased need for ancillary services related to cross-linking. “Bringing in patients for CXL evaluations—even those who have primary ophthalmologists—has increased the keratoconus population within my practice and increased the volume of related services (keratoplasty, specialty lenses, etc.),” he says.

As an investigator for the CXLUSA Study Group with seven years of cross-linking experience, Randy J. Epstein, MD, CEO of Chicago Cornea Consultants and a professor of ophthalmology at Rush University in Chicago, says the 2016 FDA approval of KXL hasn’t affected his practice. “I’m part of a clinical trial, so I’m not using the FDA-approved version,” he explains. “We’re in an FDA IND study looking at the safety and efficacy of a transepithelial corneal cross-linking system that was developed by Roy S. Rubinfeld, MD.” The current Phase II study ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03029104) identifier: NCT03029104) is enrolling 3,000 patients.

“We’ve treated over 2,000 patients in our center alone,” Dr. Epstein continues. “In that group, we’ve had four retreatments, all of which have been in patients under the age of 21. Three patients have needed corneal transplants. So we feel that our system is pretty safe and effective. The indications are keratoconus, forme fruste keratoconus, post-LASIK ec-



Outcomes of Phase III studies of Avedro’s KXL system in progressive keratoconus (red) and post-refractive surgery ectasia (pink). Treated keratoconic eyes improved by 1.6 D at one year; control eyes continued to progress. In ectatic eyes, Kmax improved by 0.7 D at one year, while control eyes worsened by 0.6 D.

tasia and visual fluctuation following RK, although we have not personally treated any patients in that last category.”

Dr. Epstein’s group favors transepithelial cross-linking in part because they say it broadens the age range of prospective patients and yields benefits faster than epi-off crosslinking. “By not removing the corneal epithelium, it significantly enhances the benefit-to-risk ratio,” he says.

He credits Dr. Rubinfeld with changing CXLUSA’s protocol to epi-on after a very short period of epi-off cross-linking. “After suffering through a month of epi-off treatments which brought us back to the PRK days of bandage lenses, pain and the whole nine yards, we were very happy to switch to epi-on and never looked back,” Dr. Epstein recalls.

He considers adequate riboflavin absorption more important to cross-linking success than removal or retention of the corneal epithelium. The CXLUSA group’s protocol relies on a customized riboflavin formulation and documentation of adequate riboflavin loading before light exposure to promote this. “The main thing that makes our study different

from most previous epi-on studies is that the requirement of our protocol has always been that the surgeon has to assess the cornea after the loading has been completed, to make certain that the cornea has in fact absorbed adequate riboflavin,” he says. “We have a flip chart that has standardized photographs of different degrees of saturation, from grade one to grade five. We aim for a grade of three to four as optimal.”

### Treat Sooner? Younger?

Keratoconus is generally a disease that starts progressing sometime in adolescence and stabilizes by the fourth decade of life.<sup>4</sup> KXL is currently approved for patients aged 14 years and up with progressive disease, although cross-linking children and adolescents soon after diagnosis without waiting for disease progression may also be safe and beneficial.<sup>5</sup>

Dr. Rabinowitz has developed criteria that help him decide when to treat. “I use a 1-D change in the steepest part of the cornea; a change in prescription, particularly in the astigmatism; third, patient complaints of worsening vision; fourth, an obvious pattern of keratoconus

on topography; and fifth, a change in OCT greater than 20  $\mu\text{m}$ ,” he says. “Only patients 14 years of age or older who demonstrate clear progression of disease are candidates for treatment.”

“I have not treated anyone younger than 14 years, but I have treated a 14-year-old. I would consider younger children and create a special consent as needed,” says Dr. Feldman. He weighs the risks and benefits before offering treatment. “I treat when I believe that the patient is at risk for vision loss and that the benefits of CXL outweigh the risks,” he says. “This generally means a patient with a history of recent progression (within the last one to two years). However, in younger patients (<21) I will treat if there is evidence of moderate disease even in the absence of progression, because these patients are at high risk for progression.”

Dr. Epstein advocates treating at younger ages as needed. “Initially, everybody thought that in terms of the actual indication for the procedure, you would have to document progression. But I don’t really think it’s ethical to make that demand for people under the age of 25, or maybe even 30,” he says. “You know it’s going to progress. If it was my kid, I don’t think I would want to sit around and wait for objective evidence of progression before I recommended treatment.

“We can treat people as young as 8 years of age,” he continues. “Most people would not be too excited about treating an 8-year-old with epi-off cross-linking. Ours is a kinder, gentler version of the procedure. We hope that the FDA eventually approves a similar system. In kids, we have the unique ability to stop a disease in its tracks.”

Dr. Hersh concurs that it is better to catch keratoconus earlier when it presents in young patients. “I personally think that it’s important to treat

younger people when they are diagnosed, because they are invariably going to worsen over time,” he says. When practicable, Dr. Hersh relies on serial topographies to help him decide when to treat. “One doesn’t simply get KC at 14 and then have it stop,” he says. “It tends to progress more rapidly when you’re younger.”

*“It’s a pretty low-tech procedure: The ultraviolet light is not an excimer laser, and riboflavin is obviously not that complicated of a molecule, so when you get right down to it, it should be something that ought to be widely available at a reasonable price. But there are a lot of factors involved.”*  
—Randy J. Epstein, MD

### Managing Expectations

After deciding when to treat, is there a way to predict which patients will respond best to cross-linking? Dr. Hersh and Steven A. Greenstein, MD, published a multifactorial analysis<sup>6</sup> of 104 eyes to see if they could find predictors of how individual patients would fare post procedure. “With regard to actual improvement in corneal topography, we found that patients

who had steeper cones—patients we defined as 55 D or more—were more than five times more likely to improve by 2 D or more,” he says. “However, we didn’t find any indicator for failure of the procedure to diminish progression. But generally, patients who were worse tended to have a more appreciable improvement. Similarly, looking at corrected vision, most patients stayed the same, but we had about 25 to 30 percent who got more than two lines better; the primary predictor of that was a worse baseline visual acuity. Patients who were 20/40 or worse were about five or six times more likely to improve by two lines or more, compared to those who were better off to start with.

“We also noted a little trend in patients who had very good vision: They were at slightly greater risk of losing one line of vision with the procedure,” adds Dr. Hersh. “I think these are all variables that those beginning cross-linking need to understand and discuss with their patients when determining who should have it done and why they are having it done.”

Although cross-linking can afford patients better visual acuity and function, all four doctors stress to their patients that these are not the definitive goals of treatment. “What we tell patients and their families—and what a lot of my colleagues don’t realize—is that there are three goals of this procedure,” explains Dr. Epstein. “The first goal is to stop the progression. The second goal is to enhance contact lens tolerance. We tell them all going into it that this is our actual objective, because there are a number of studies that have been published showing a fairly dramatic impact of corneal cross-linking on the anterior cornea, both with regard to the keratocytes and more importantly, the corneal nerves, so many patients who have previously been ‘contact-lens intolerant’ find that they can effectively wear con-



tacts. In our practice, our optometrists are able to fit 95 percent of our treated patients successfully. The third objective is to get some improvement in vision,” he says.

Dr. Epstein also notes that most of his patients do report rapid onset of visual improvement, thanks to leaving the epithelium intact. “Most of our patients tell us as early as the next day that they are already seeing better, either with their glasses or when they put on their old contacts, and that’s something we haven’t been able to explain very well,” he says.

“Cross-linking is not designed expressly to help vision, but to halt progression,” stipulates Dr. Rabinowitz. “A small percentage of cross-linking patients do get somewhat improved vision, but I don’t like to tell my patients that. I don’t know who’s going to get improved vision and who isn’t; so if they went in expecting improved vision and they didn’t get it, they would be very disappointed. It’s better for me to tell them, ‘Look, this will stop the progression of the keratoconus, but if you want to make your vision better, then we’ll do INTACs combined with cross-linking.’”

### CXL Plus INTACs, Maybe More

As previously mentioned, Dr. Rabinowitz is currently investigating the use of INTACs after cross-linking. “If you combine it with the INTACs, then you actually get improvement of the vision,” he says. “Our study involves comparing a combination of INTACs and cross-linking to cross-linking alone. We’ve found that if you combine the two, the visual outcomes are actually quite a lot better. I have followed some patients for as long as eight years. Follow-up is ongoing—about a 10-year cycle—because we really want to see what happens long-term.”

Dr. Rabinowitz doesn’t perform the INTACs procedure immediately



Brad H. Feldman, MD

Adequate riboflavin loading prior to UVA light exposure is crucial to ocular safety and a good outcome, regardless of the corneal collagen cross-linking protocol employed.

after cross-linking, however. “I like to wait three to six months after doing cross-linking before I do the INTACs,” he says.

Dr. Epstein also adds INTACs after cross-linking to improve patients’ visual outcomes. “If they’re not fittable with contacts, or if they want to take it to the next level visually, they can have INTACs put in after they’re cross-linked,” he says.

“INTACs are meant to change the corneal topography even more dramatically than cross-linking,” says Dr. Hersh. “We do them on a fairly frequent basis because they tackle a problem that KC patients have, separate and distinct from stability, and that is the need to improve corneal topographic asymmetry. Indeed, with the techniques we’re using now, we can achieve upwards of 7 D of improvement in the corneal topography, both flattening the cone and restoring corneal symmetry with improved superior-to-inferior ratio.” Dr. Hersh adds that he’s involved in a clinical trial seeking to determine how well INTACs and cross-linking work together, as well as whether INTACs procedures should be done concurrently with cross-linking, or three months post-CXL.

Cross-linking for infection control, or PACK-CXL (photoactivated chromophore for infectious keratitis cross-linking) is one application that has not yet convinced Dr. Hersh of its efficacy. “With regard to infectious keratitis, published results have

been very equivocal thus far,” he says. “It seems that it’s more effective in earlier, more superficial infections, but a lot more work really needs to be done to determine if it’s really efficacious.”

Dr. Epstein’s study colleagues have had some experience with the use of cross-linking for infection control, but he’s skeptical. “We actually had an arm of our earlier IRB study where a number of the centers—ours not included—were doing it for therapeutic indications. The results were not very impressive, and there were just so many confounding factors that I have a hunch that it’s not going to pan out to be a big deal,” he says.

He’s keen on the potential of combining refractive procedures with cross-linking to maximize visual improvement, however. Dr. Epstein relates that one of his patients, after cross-linking and INTACs, went to other surgeons for subsequent toric ICLs and topographically guided PRK to achieve spectacle and contact lens independence. “That shows how far you can carry things,” he says. “We just started doing topographically guided PRK and LASIK treatments with our Wavelight Allegretto laser, and we’re cautiously optimistic that we may be able to use at least some elements of that to at some point start doing custom topographically guided PRK on patients with keratoconus who have previously been cross-linked. That’s really our

ultimate goal. That's off label, and I don't anticipate an approval. But it's an exciting possibility," he says.

Dr. Hersh anticipates the expansion of corneal cross-linking in combination with therapies that will improve vision in newly stabilized eyes. "I think you're going to find increasing interest in topography-guided PRK and PTK as adjuncts to cross-linking, to further improve the corneal topography. In addition, we'll do ICLs with great success in many keratoconic patients who are stabilized with cross-linking," he says. Dr. Hersh is also participating in a study looking at the implantation of preserved corneal tissue to improve corneal topography, thickness and regularity in cross-linked eyes.

### Is Access a Challenge?

For all its promise, many American surgeons are still integrating the FDA-approved cross-linking protocol into their practices—and hoping it will be accessible and economically viable. Effective July 1, 2017, Avedro hiked prices for the KXL system's two photosensitizing agents, Photrexa and Photrexa Viscous, from \$595 to \$2,850. Prior to this, a Dutch study attempted to estimate the cost of Dresden protocol cross-linking in the health-care setting, and postulated that the total cost of the procedure for one eye, inclusive of pre- and postop care, was about \$1,929.47 ± \$194.95.<sup>7</sup>

"It's a pretty low-tech procedure: The ultraviolet light is not an excimer laser, and riboflavin is obviously not that complicated of a molecule, so when you get right down to it, it should be something that ought to be widely available at a reasonable price. But there are a lot of factors involved. We do a fair amount of discounting for indigent patients," says Dr. Epstein, who is involved in a clinical trial and doesn't use the KXL

system or the Photrexa drugs.

"Either insurance companies will choose to set a very high reimbursement fee for the procedure (much higher than what insurance companies have reimbursed thus far), and we will be able to offer the treatment to all patients, or the insurance reimbursements will be too low and providers will only offer this as a cash procedure. This will severely limit access to treatment for the majority of keratoconus patients—as has been the case now for years. This would be a terrible outcome," opines Dr. Feldman.

"Access is a challenge for patients and for doctors," adds Dr. Rabinowitz. "Because offering the procedure is expensive, the physician has to do a significant volume to pay for the overhead. It takes a lot of chair time—at least an hour to an hour and a half. I think the whole issue of fees is still evolving."

Dr. Feldman stresses that guiding preoperative patient expectations and following up postoperatively are costly extensions of the considerable intraoperative chair time that cross-linking requires. "To offer patients the highest quality experience, you need to spend a lot of chair time with them preoperatively and postoperatively," he explains. "Often, patients arrive believing that CXL is a 'cure' that will provide them with normal vision; many believe this is like LASIK. There is almost always worsening of vision transiently after the treatment, with visual improvement typically delayed until several months out. This requires much handholding. Patients who are contact lens dependent are also forced out of contacts for significant periods of time or need re-fits, and this creates a situation where patients are out of work, sometimes for weeks. This again requires plenty of time for communication as well as paperwork."

Whether and when cross-linking becomes accessible to all patients who could benefit from it remains an open question, but its very availability is a game changer. "Cross-linking is a great new improvement," Dr. Hersh observes. "It really tackles the most important thing that we need to address in ectatic corneal processes, and that is keeping patients from progressing until they can no longer see well and are in need of corneal transplant. There are also adjunctive procedures that may further improve corneal and visual rehabilitation. There is a lot that we'll be seeing on the keratoconus frontier." **REVIEW**

*Dr. Rabinowitz reports no financial interests related to cross-linking or any of the associated products mentioned in this article. He has received NIH funding for a study of the genetics of keratoconus through the NEI for 23 years. Dr. Hersh was the medical monitor for the Avedro KXL/Photrexa/Photrexa Viscous clinical trials. Dr. Feldman has not reported relevant financial interests. Dr. Epstein is a consultant for Alcon and Shire, but has no financial interests in products related to cross-linking.*

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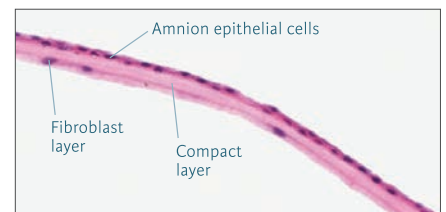
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TGF- $\beta$ 1	+	+
<b>Interleukins</b>		
IL-4	+	+
IL-6	+	+
IL-8	+	+
IL10	+	+
<b>Tissue Inhibitors of Metalloproteases</b>		
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# Work Up Corneal Ulcers Like an Expert

Walter Bethke, Editor in Chief

The best ways to diagnose and heal a corneal infection.

The diagnosis and management of a suspected corneal infection can be a lot like entering a maze: You have no map to your destination and many promising pathways turn into disappointing dead ends. You don't have to get lost amid myriad details from the patient's history and exam, however. In this article, corneal specialists detail how they diagnose and treat corneal ulcers, in the hope of giving you some much-needed direction in your search for a cure.

## Deciding Factors

Though corneal specialists usually see ulcers when they're at advanced stages, rather than just suspicious specks, they can shed light on what the comprehensive ophthalmologist should watch for in the patient history and exam in order to root out the cause of the patient's complaint.

- **History.** "The first-, second-,

third- and fourth-most important question to ask is: 'Are you a contact lens wearer?'" says Sadeer Hannush, MD, attending surgeon at the cornea service at Wills Eye Hospital and medical director of the Lions Eye Bank of Delaware Valley. "Contact lens wear is the most common cause of infectious keratitis. If the patient says, 'Yes,' you can then try to identify a breach in contact lens-care protocol by asking questions such as, 'Do you sleep in them? Are you cleaning them correctly? Do you swim in them?'"

Christopher Rapuano, MD, director of Wills Eye Hospital's cornea service, adds that showering in contact lenses isn't that great, either, though some patients do it. "I also ask, 'How old are is the contact lens that you put in the eye?'" Dr. Rapuano says. "Just this morning I saw a patient who had been sleeping in the same contact lenses for three months straight."

If the patient isn't a contact lens wearer, there are other avenues to explore in the history. "In that case, look for other causes, such as trauma from a child's fingernail, a mascara brush or working under a car," Dr. Hannush notes. Physicians also note that a particular kind of injury can lead to a certain type of organism getting into the cornea. An injury from a plant or an animal, or from something that caused

A large central *Scedosporium* fungal corneal ulcer with a small hypopyon. Note the irregular edges of the infiltrate.



All images: Christopher Rapuano, MD

a foreign body from the ground to be thrown into the patient's eye are often behind fungal infections, and exposure to fresh water is a risk factor for *Acanthamoeba*. Also, ask about prior surgery, as both cataract and refractive procedures are predisposing factors to corneal infections.

Another important part of the history, at least from a corneal specialist's perspective, is whether the patient has already been treated with something for the condition. "Some patients are on antibiotics—sometimes fortified antibiotics—antifungals, anti-ameobic medications or antivirals," says Dr. Rapuano. "Some patients come in on all of them! Their referring doctor threw the whole pharmacy at them, hoping something would work." Dr. Rapuano adds that he also focuses on when the symptoms started. "If the symptoms started a day ago, that gives me a different differential diagnosis than if it was a week or a month ago," he says.

• **Exam.** Bennie H. Jeng, MD, chair of the Department of Ophthalmology and Visual Science at the University of Maryland School of Medicine, says it's important to initially confirm that you are indeed dealing with an infection. "First, when examining the patient, determine if it looks infectious or not," Dr. Jeng says. "Sometimes a sterile infiltrate might look like an infection when in fact it's just inflammation in the cornea. An ophthalmologist might see contact-lens-related sterile infiltrates that appear in the periphery due to such things as contact lens overwear and hypoxia. The challenge, then, is to understand the risk factors well enough, and be comfortable enough with the clinical appearance, to know when an infiltrate is probably inflammatory, and to treat it with steroids, not just antibiotics."

The level of visual acuity is important, as well. "If it's 20/20 and the patient has a little peripheral ulcer, I'm not as concerned as I would be if it's

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hand-motions with a large central ulcer,” Dr. Rapuano says. “How do the lids look? Do the lids have ulcers on them? Did the patient have shingles recently? Do the lids close properly? If they don’t, this can lead to problems due to exposure. At the slit lamp, get an idea of the size, density and location of the ulcer. If it’s in the middle of the cornea, that’s more concerning than if it’s in the periphery. Gauge how much inflammation is in the cornea and how thin it is. If it’s a bad ulcer that’s eaten away 95 percent of the cornea and is about to perforate, that puts it in a different category than a small, peripheral infiltrate with no ulceration that’s not thinning the cornea at all. Next, look for inflammation in the eye itself; are there lots of anterior chamber cells? Does the patient have a hypopyon? Also, check the intraocular pressure. When there’s a lot of inflammation, the IOP is most likely pretty high and needs to be managed.”

Dr. Hannush says if the ulcer is vision-threatening, the general ophthalmologist will almost always refer the patient “because the standard of care for a vision-threatening ulcer is culturing, and most general ophthalmologists aren’t equipped to culture.”

“The next question is what’s the etiology,” says Dr. Jeng, who notes that some presentations can be deceptive. “We often see recurrent herpes simplex virus keratitis manifest in the stroma as an immune process, and it’s actually treated with steroids. However, let’s say we don’t think it’s viral, but it’s more like a classic bacteria or fungus. There are certain characteristics that can point us in one direction or another. For instance, textbooks will tell you that a feathery infiltrate with satellite lesions and a plaque on the endothelium is fungus, and in a lot of cases it is. However, it can be bacterial.

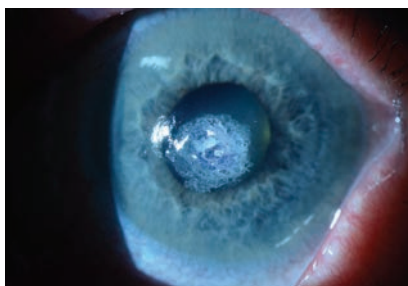
“The patient’s condition is also a clue,” he notes. “For example, say someone who is on chronic topical antibiotics and steroids develops an



A small, deep corneal ulcer that has caused a central corneal perforation. The striae radiating from the ulcer indicate deep involvement or even perforation.

infection: This eye is in a local immunocompromised state, and the infection could be fungal. The environment where you practice is also a factor. For instance, in the Northeast U.S. or northern California, it’s unusual for us to encounter a fungus, and often there’s some specific reason for it when we do, such as a patient on chronic steroids or who is immunocompromised in some way. In those cases we’d think more along the lines of *Candida* or a yeast infection. If you’re in Miami, however, where it’s hot and humid, ophthalmologists see more fungus, so they have to have a higher suspicion for it, and the fungus is usually not the indolent yeast but rather the more aggressive filamentous variety.”

Dr. Rapuano says *Acanthamoeba* can cause specific findings if you know what to look for. “On the history, patients often say that it’s been going on for weeks,” he says. “They may have



Cyanoacrylate tissue glue was used to treat the perforated ulcer in the previous image, after which a bandage soft contact lens was placed. Small air bubbles can be seen under the contact lens.

already been treated for herpes infection, because *Acanthamoeba* resembles it. Also, they often have an extreme amount of pain, well out of proportion with the clinical findings and exam. In such cases, I’ll do the cultures, but I’ll also send some specimens to the pathology lab to look for *Acanthamoeba* cysts in the epithelium.”

• **Culturing and management.**

Corneal specialists say the next decision, for them, would be whether to culture the organism, and for the comprehensive ophthalmologist, whether to refer the patient for culturing. Dr. Rapuano explains how he approaches the issue. “Things that push me to culture: the more central it is; the bigger it is; the more ulcerated it is—all these things make it worse and more likely for me to culture it,” he explains. “Also, I’ll culture it if there’s an unusual history that would make me suspect fungus or *Acanthamoeba*. In terms of ulcer size, if it’s under about 2 mm in diameter, I tend not to culture. If it’s larger than that, I tend to culture. This is a guideline, though, and not absolute.”

Dr. Hannush acknowledges that the general ophthalmologist usually isn’t set up to culture, and will usually start the patient on a broad-spectrum antibiotic. “Most use a fourth-generation fluoroquinolone,” he says, “or a very good wide-spectrum drug, Polytrim, which is trimethoprim and polymixin. Trimethoprim is a very good gram-positive-coverage drug, especially for MRSA. Polymixin is a decent gram negative drug, but not great. Moxifloxacin used to be the most popular because it had good gram positive and negative coverage. Gatifloxacin probably has a little bit better *Pseudomonas* coverage. Obviously, if you’re concerned about a contact lens-related ulcer, then *Pseudomonas* is number one on your list until proven otherwise. For *Pseudomonas*, if you’re not giving fortified antibiotics, consider gatifloxacin, ciprofloxacin and tobramycin.”

Dr. Hannush says the corneal spe-



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cialist will also follow this course for patients with no topical antibiotics already on board and for whom the ulcer isn't vision-threatening. If there's significant anterior chamber reaction, hypopyon or an ulcer close to the visual axis, he says corneal specialists will scrape, culture and start the patient on fortified antibiotics. "Fortified antibiotics are usually tobramycin 14 mg/cc and either cefazoline 15 mg/cc or vancomycin 25 mg/cc," he notes. "All three of these products need to be prepared by a compounding pharmacist."

Treatment protocols can vary. "I'll prescribe the drugs for use every half hour while awake and every two hours throughout the night," says Dr. Hannush. "I never do every hour during the night because it makes patients totally exhausted. I also try to separate the drops' timing so they don't wash each other out." Dr. Hannush then sees the patient after one or two days. "The first sign of recovery is a decrease in pain," he explains. "This can occur even when the ulcer doesn't look any better. After that, the next sign is re-epithelialization and resolution of the hypopyon. The hypopyon first gets organized—meaning it's not liquid anymore. You don't see a level to it, but instead it just looks like a mass in the inferior angle. Eventually, the corneal infiltrate starts dissolving."

If cultures were done, sub-specialists say they'll adjust the medications based on the culture results for maximum efficacy. "If it proves to be fungal, we'll shift medications significantly," says Dr. Rapuano. "They get natamycin if it's *Fusarium*, though a lot of pharmacies don't carry it so it's not always easy to find. If it's *Candida*, you usually can put them on a compounded amphotericin drop. If the specimens at the pathology lab test positive for *Acanthamoeba*, or I have a high suspicion for *Acanthamoeba*, I'll start them on Brolene and Baquacil, specially compounded."

Corneal specialists also note that steroids may play a role in the treatment

of some ulcers, though they have to be used carefully. "After a few days, if the infection's under control, we know what we're treating and the patient's on the appropriate antibiotics, you can think about starting some steroid drops," he says. "Steroids are a double-edged sword, though, in patients with infections. We don't use them early for *Acanthamoeba* or fungus. In bacterial infections, however, some can respond nicely if there's a lot of inflammation, since it can improve with judicious use of steroids. Patients on steroids have to be followed very closely, and you have to stop the steroids if it looks like they're making things worse. When to start the steroids, if you use them at all, depends on the patient. It can be two or three days to a week after treating the infection. For this application, we'll often use Lotemax or Pred Forte t.i.d. or q.i.d. and see how they do."

Over the next one to three weeks, Dr. Rapuano will slowly decrease the medications and add a nighttime ointment to replace the drops administered throughout the night. "We'll start a nighttime ointment such as gentamycin, ciprofloxacin, polysporin or the like and then slowly decrease the meds during the day," he says. "We'll stop the steroid drop, too, once the inflammation is improved, and go from there."

### Tough Cases

In some cases, organisms prove hard to kill or wounds don't heal. Here's how to respond.

• **Switch drugs.** Dr. Hannush says that, in some cases, the organism may be different than you first expected. "If, for example, the patient's on fortified tobramycin/vancomycin and there's no response, you have to re-scrape and culture," he says. "I just had a case like this. I rescraped and suspected a fungal ulcer, so I empirically started the patient on topical voriconazole 1% and he started getting better."

• **Emergency transplants.** "If they're not getting any better, you can reculture," says Dr. Rapuano. "Or you might determine that it's just too deep and isn't showing up on culture, so you can do a biopsy: go down one-third to one-half corneal thickness with a punch and send half to pathology and half to the culture lab."

"If they're perforated," Dr. Rapuano continues, "and it looks like it's just a small perforation in the cornea, you can use some glue to seal the perforation if you think the infection's getting better. Often, though, you have to do an emergency—or 'hot'—transplant." He says these transplants can be small if the perforation is small and in the periphery, but often they need to be big since they're often used for large central ulcers. It's also better not to wait too long to do it, since the ulcer grows over time. "These transplants have a pretty good success rate for resolving the infection, but they often get cloudy and need to be repeated six to 12 months later," he says.

• **Non-healing wound.** Dr. Rapuano says that, in some rare instances, he's able to kill the organism in the cornea but the infection did so much damage to the tissue that the surface is having a difficult time healing. "When we've treated the infection and it looks like it's getting better, but the corneal scratch isn't healing well, we'll use amniotic membrane," he says. Options for this include cryopreserved membrane such as ProKera and dehydrated membrane such as AmbioDisk, OculoMatrix, BioDOptix or Aril. "Using the membrane is pretty straightforward," Dr. Rapuano says. "There's not a large learning curve. Some physicians glue them on, some suture them, and some use several layers." **REVIEW**

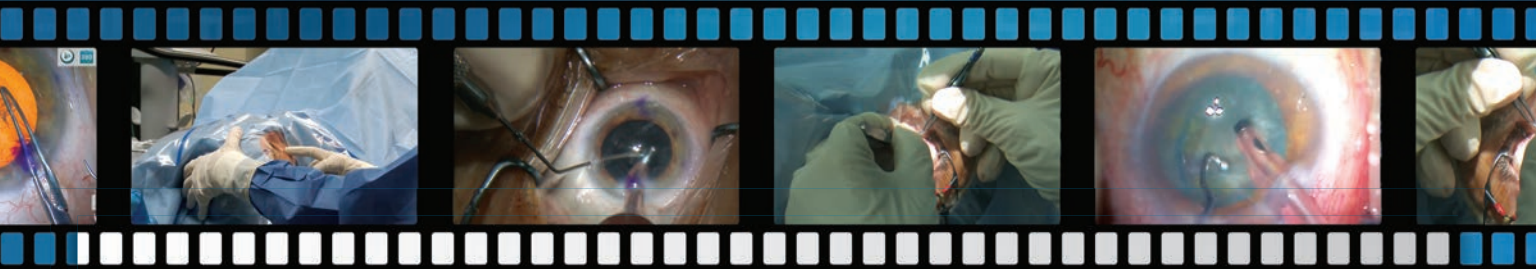
*Dr. Rapuano has consulted for Allergan, Bausch + Lomb and Bio-Tissue. Drs. Hannush and Jeng have no financial interest in any products discussed in the article.*



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# How to Manage Conjunctivochalasis

*Benjamin B. Bert, MD, FACS, Fountain Valley, Calif.*

Tips for diagnosis,  
as well as medical  
and surgical  
management.

Unfortunately, as we age our body's tissues lose their elasticity. The ocular surface is not exempt from this phenomenon, and one of the most common signs of this degradation is conjunctivochalasis. In 1942, Wendell Hughes, MD, coined the term conjunctivochalasis, meaning relaxation of the conjunctiva.<sup>1</sup> However, the entity itself was described previously by Anton Elschnig, MD, in 1908 as loose, nonedematous conjunctiva.<sup>2</sup> We currently define conjunctivochalasis as loose, redundant conjunctiva, most often located on the inferior globe. In this article, I'll describe the defining characteristics of conjunctivochalasis and review the best ways to treat it.

## Diagnostic Features

While conjunctivochalasis increases in incidence and magnitude with age,<sup>3</sup> its appearance and location can vary. On average, it's more common to see conjunctivochalasis of the inferotemporal bulbar conjunctiva than inferonasally.<sup>4</sup> Many of the symptoms of conjunctivochalasis are similar to the complaints in dry-eye disease, including eye pain, blurred vision, epiphora, dryness and the presence of subconjunctival hemor-

rhages. If these symptoms worsen in downgaze, it's more likely that they're due to the redundant conjunctiva in conjunctivochalasis.<sup>4</sup> Another difference from most forms of dry eye is that the blurred vision and eye pain actually worsen with frequent blinking. One explanation for this phenomenon is that the upper eyelids are not dipping into the inferior tear meniscus, but only touching the redundant conjunctiva and then returning to their open position without spreading a new tear film over the ocular surface. Combining a faster tear breakup time<sup>4</sup> with compromised tear-replenishing puts symptomatic conjunctivochalasis patients at a distinct disadvantage when it comes to ocular surface comfort.

In regards to epiphora, conjunctivochalasis is hypothesized to contribute in two ways: First, the duplicated folds of conjunctiva disrupt the inferior tear lake (*Figures 1 and 2*) and, second, the conjunctiva itself can cause a mechanical blockage of the inferior punctum.<sup>5-6</sup> Blockage of the lower punctum is more common with nasal conjunctivochalasis or with gaze toward the punctum. Dr. Yan Wang and her group at Japan's Keio University showed that blockage of the tear drainage keeps inflammatory cytokines on the ocular



Figure 1. Mild conjunctivochalasis seen with normal illumination. It can be difficult to see the folds when they are this mild. However, this patient was still symptomatic with epiphora and no corneal staining.

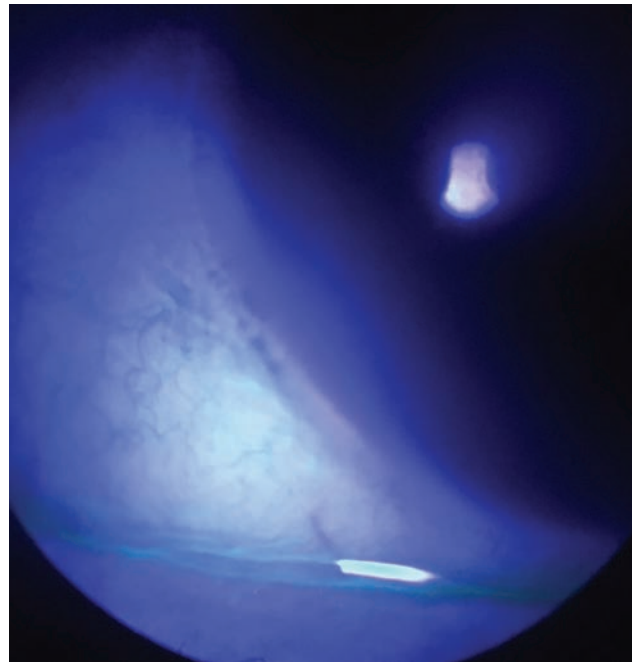


Figure 2. The patient from Figure 1 seen with fluorescein dye and a cobalt blue filter. The conjunctival folds and their obliteration of the tear lake are more easily identifiable.

surface longer, in particular interleukin-1 $\beta$  and TNF- $\alpha$ . Dr. Wang hypothesized that the prolonged contact with these inflammatory markers can lead to increased discomfort and the activation of MMP-1 and MMP-3 in conjunctival fibroblasts, causing additional breakdown of the conjunctival elasticity and furthering the progression of conjunctivochalasis.<sup>7</sup> This hypothesis would contraindicate one of the standard treatments of dry-eye disease, which would be to place punctal plugs and purposefully obstruct tear outflow.

## Treatment

One of the most frustrating things about treating patients with ocular surface complaints is that they're chronic and can be refractory to many treatments. Closely examining these patients can allow for targeted treatment that can start the patient in the right direction early on

in their disease course. Though not all patients with conjunctivochalasis will have symptoms, a patient who's complaining of burning, irritated or dry eyes should be examined closely for the presence of conjunctivochalasis. Using the following options, the treatment can be tailored to the patient and his specific pathology, yielding a better chance for success.

## Medical Treatment

Before proceeding to surgery, it's prudent to try to first medically treat the patient's symptoms. Here's how to approach the different severities of conjunctivochalasis:

- **Mild.** If patients are asymptomatic then they can simply be observed. The finding of conjunctivochalasis alone does not warrant treatment.

- **Moderate.** When patients become symptomatic, the first line of treatment is medical. The goal is to

reduce the effects of conjunctivochalasis, especially in regards to the disruption of the tear film. Lubricants tend to be the first-line medications, and while there have not been specific studies looking at different viscosities and their effects, I tend to utilize the gel drop as first-line treatment for these patients. The rationale for doing this is that the inferior tear meniscus has been obliterated by the multiple folds of conjunctiva and is not providing a supply of tears to be spread during the patient's blink. Thin tears would continue to be disrupted by the conjunctival folds. However, more viscous drops are able to stay suspended on the surface of the conjunctiva and act in a fashion similar to a tear lake.

- **Severe.** In severe cases in which the conjunctivochalasis causes the conjunctiva to be exposed even when the eyelids are closed, using artificial tear ointment and patching the eyes at night can be beneficial.<sup>8</sup> These

patients may also need to use the ointment during the day if they have significant desiccation of the exposed conjunctiva.

In addition to the medical approaches described, any other underlying inflammatory conjunctival conditions should be treated to assist in controlling the patient's symptoms. This includes treating allergic inflammation with topical antihistamines/mast cell stabilizers, and generally increased inflammation with topical steroids.<sup>8</sup> If patients remain symptomatic despite medical treatment, then surgery becomes a reasonable option.

## Surgical Treatment

When drugs aren't enough, it's time to move on to a surgical solution. Here's the best way to proceed.

The first step of any surgical procedure is informed consent. However, trying to explain exactly what conjunctivochalasis is to a patient can be challenging. Often, patients think of the conjunctiva as the "white part of the eye." You may find yourself trying to correct that belief by explaining that it is actually a semi-transparent mucous membrane over the sclera, the "true" white part of the eye. Just explaining the anatomy typically requires more time than is available, and when you're done you still haven't even discussed the actual disorder or its treatment. To help in this situation, I find that it is easiest to explain to the patient using the analogy that conjunctivochalasis is like loose belly skin. Instead of skin hanging over the belt or the band of the pants, the redundant conjunctiva hangs over the lower lid. Just as there is occasionally the need for a "tummy-tuck," they'll understand the analogy to a "conj-tuck."

There are a number of different techniques that have been described to correct conjunctivochalasis. Some

of these are minimally invasive and can be done in the office, while others require a controlled environment, like a procedure room or operating room.

- **Cautery approaches.** Most of the in-office procedures involve some type of thermally-induced shrinkage or excision to get rid of the redundant folds of conjunctiva clinically visible and resting on the lower lid. One study described using thermocautery as a way to excise the excess conjunctiva at the slit lamp with results showing greater than 90-percent improvement in both subjective and objective findings.<sup>9</sup> Their technique involved grasping the redundant conjunctiva with smooth forceps and then excising the grasped portion with a handheld low-temp cautery. There was scarring noted postoperatively in 15 percent of their patients, but it didn't have any sequelae.

Diana Muñoz, MD, and her colleagues in Bogota, Columbia, describe using a bipolar electrocautery forceps to apply the treatment directly to the symptomatic fold itself, which they identify by positive lissamine green staining. The procedure uses a traction suture through the inferior limbus to rotate the eye superiorly, so this may best be done in a controlled environment. After anesthetizing the area, the stained portion of conjunctiva is elevated and its base is grasped using the bipolar forceps. Energy is applied to the area directly at a rate of 30mA until "complete shrinkage" is achieved. The benefit of this technique is that you target the exact area the symptoms are coming from for that individual patient, whether it is nasal, inferior or temporal. Dr. Muñoz's group noted that all of their patients had complete resolution of their symptoms without scar development.<sup>10</sup>

- **Argon laser.** Argon laser has also been used to "shrink" the redundant conjunctiva. In South Korea,

Sangkyung Choi, MD, and his group describe using a 532-nm argon green laser set at 500 μm and ranging in power from 600 to 1200 mW for a duration of 0.5 seconds to treat the inferior conjunctiva. They apply approximately 100 burns during the treatment using "proper shrinkage" as the endpoint for their procedure. Their results showed a statistically significant improvement in the Ocular Surface Disease Index and in tear breakup time, improving from 9.2 seconds to 10.2 seconds. The treatments were more successful in mild and moderate cases.<sup>11</sup>

- **Incisional/glue approaches.** In the operating room, the redundant conjunctiva can be removed in a number of ways previously described in the literature, including: simple excision with direct closure;<sup>6</sup> injection of fibrin glue subconjunctivally, then pinching and excising;<sup>12</sup> as well as a technique in which a limbal peritomy is made with radial relaxing incisions, allowing the loose conjunctiva to be pulled anteriorly and excised with subsequent approximation of the cut edge of conjunctiva to the limbus.<sup>13</sup>

However, the most highly recommended surgical procedures not only excise the redundant folds of the conjunctiva or tighten it, but also reestablish the fornix. This is because if excision alone is performed, one of the possible complications is scarring leading to foreshortening of the fornix and the possible development of a cicatricial entropion. It's now believed that, when attempting to improve the function of the tear film, returning the depth of the fornix to its physiologic baseline is as important as removing the redundant conjunctiva. Scheffer Tseng, MD, and his group at Bascom Palmer showed that the tear reservoir in the inferior fornix will rapidly replenish the tear meniscus in normal patients, but that this process is blocked by



the additional redundant conjunctiva in the fornix of conjunctivochalasis patients.<sup>14</sup> The group showed that repairing this surgically and deepening the inferior fornix reestablishes the normal function of the reservoir and thus provides better resolution of dry eye and ocular surface discomfort symptoms than excision alone.

Dr. Tseng describes being able to normalize the fornix during excision of the conjunctiva by making a crescentic excision of the loose inferior bulbar conjunctiva starting with a peritomy approximately 2 mm posterior to the limbus. He excises all of the loose and thin conjunctival tissue, allowing the remaining conjunctiva to recess into the fornix. The bare scleral defect is then covered with cryopreserved amniotic membrane and anchored using either sutures<sup>15</sup> or fibrin glue.<sup>16</sup> Glue has become preferred due to less inflammation and better patient comfort. In a retrospective review by Dr. Tseng's group, there was significant improvement in dry-eye symptoms and clinical findings. An added benefit was that 56 percent of their patients who had a prior diagnosis of aqueous-deficient dry eye, which they termed aqueous tear deficiency, had normalized on their fluorescein clearance testing.<sup>17</sup> They hypothesize that the conjunctivochalasis caused so much disruption and blockage in the fornix that it had created an aqueous-deficient state.

Ocular surface discomfort is a common and often frustrating condition for both patients and physicians. It's important to look at the entire ocular surface to diagnose and appropriately treat a patient's symptoms. With targeted treatment, there is a much better chance for success. To that effect, don't overlook the amount that conjunctivochalasis contributes to these symptoms. After trying conservative management with topical medications, if a

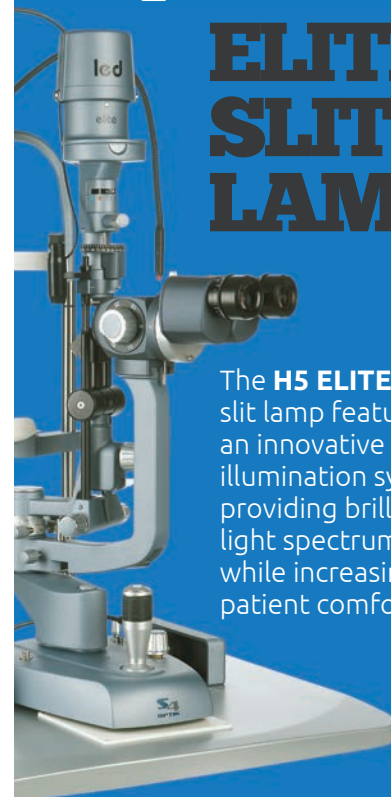
patient is still symptomatic, then it's beneficial to take them to the operating room. While all of the surgical procedures discussed here produce great outcomes, I would recommend excision of the redundant and loose conjunctiva with the attempt to reestablish the normal contour of the inferior fornix. By surgically returning the ocular surface to a more normal state, we help to create an environment in which it's easier for the body to maintain homeostasis. **REVIEW**

*Dr. Bert is a Health Sciences assistant professor at the Doheny and Stein Eye Institutes, David Geffen School of Medicine, UCLA. He has no financial interest in any product mentioned.*

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# Pediatric Idiopathic Intracranial Hypertension

Many ophthalmologists are well-versed in IIH in adults, but pediatric IIH is a different animal.

*Christopher M. Fecarotta, MD, Dothan, Ala.*

**I**diopathic intracranial hypertension is a condition characterized by abnormally elevated intracranial pressure without any evident neurologic or radiologic cause. Although the epidemiology, demographics and spectrum of clinical presentation of older children with IIH tend to mirror those of adults, those of prepubescent children are unique, and likely represent a separate disease entity. This article will explore the characteristics of this unique disease.

## Epidemiology

Idiopathic intracranial hypertension was originally described in adults in 1893 and labeled “meningitis serosa,” but has also been called “pseudotumor cerebri” and “benign intracranial hypertension.”<sup>1</sup> The incidence is approximately one in 100,000 individuals and can occur in all age groups, either gender and both obese and non-obese patients.<sup>2</sup> Typically, however, the presenting patient is an overweight female of childbearing age. The most common symptoms

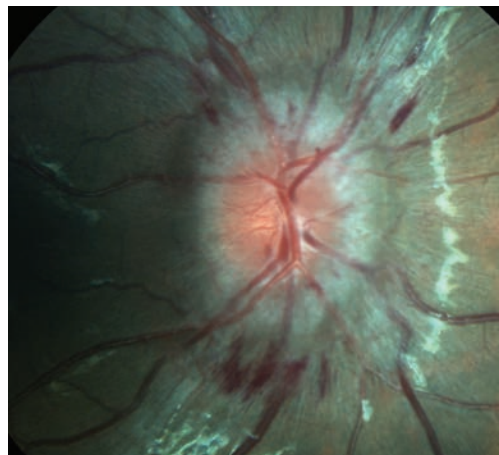


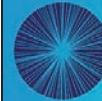
Figure 1. Fundus photograph illustrating optic nerve edema with retinal hemorrhages in a 12-year-old boy with IIH.

include headache, binocular horizontal diplopia from bilateral sixth nerve palsies, pulsatile tinnitus and vision loss from papilledema-induced optic atrophy (See Figure 1).<sup>3</sup> However, the original modified Dandy criteria for diagnosis didn’t include specifics for children.

IIH occurs most commonly in young adults, and is rare in patients over age 45 or younger than age 3.<sup>4</sup> There is no racial predisposition for the disease. No genetic cause has

been described, although familial cases have been reported. Overall, the incidence of IIH in children is from 0.5 to 0.9 cases per 100,000. Among adults, overweight females have a strong predilection for the disease; in fact, the incidence rises to 19.3 per 100,000 in women who are 20 percent or more over their ideal body weight.<sup>5</sup> Two-thirds of men and 90 percent of women with IIH are obese.<sup>4</sup>

In contrast, recent studies have shown that this disease doesn’t follow the same demographics in children as in adults. A study of pediatric patients with IIH recently demonstrated that only 43 percent of prepubertal children, compared to 81 percent of children aged 12 to 14 and 91 percent of teenagers aged 15 to 17, were obese.<sup>6</sup> The same study also reported that only half of children with IIH under 12 years old were girls, while females comprised 88 percent of those IIH patients age 12 to 14, and 100 percent of those older than 14. The unequal sex distribution and the predilection for overweight patients seems to only begin after puberty, likely as a result of



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hormonal changes.<sup>7,8</sup> Based on these findings, it appears that in the prepubescent population, the predilections towards obesity and female gender do not apply, and these risk factors may not be helpful clinical markers.

## Pathophysiology

It is generally believed that the ultimate pathophysiology behind IIH leads to either increased cerebrospinal fluid production by the arachnoid villi or decreased absorption by the choroid plexus; however, despite many different theories, the precise pathway leading to IIH is unknown. Several studies support the hypothesis of increased cerebrospinal fluid production as the crucial pathophysiologic dysfunction in IIH. Studies have demonstrated decreased CSF protein concentration in patients in the adult and pediatric populations with IIH, suggesting increased CSF production.<sup>9,10</sup> However, another study did not confirm this correlation between increased opening pressure and CSF protein concentration.<sup>11</sup> Intracranial venous hypertension is a well-established finding in IIH, but it is unclear whether it is the cause or the result of increased ICP. Another hypothesis postulates that obesity leads to increased thoracic pressure, which causes an increase in both intracerebral venous pressure and ICP. A metabolic etiology has also been hypothesized, as numerous hormones, including cortisol, thyroid hormone, growth hormone and aldosterone are known to interact with receptors similar to transporters in the choroid plexus.<sup>12</sup> Another mystery of IIH involves the ventricle. Despite the increase in ICP, ventricles in IIH do not increase in size.<sup>4</sup>

Vision loss in IIH is caused by compression of the optic nerve, as increased ICP is transmitted down the optic nerve sheath. Sixth cranial nerve palsies are the result of transmission

of increased ICP to the abducens nerve as it travels through Dorello's canal.

## Secondary Causes

Vitamin A toxicity has long been known to cause IIH. This association was first reported amongst explorers consuming polar bear liver, which has very high levels of vitamin A.<sup>13</sup> Medications containing vitamin A are commonly prescribed to adolescents for acne. Tetracycline antibiotics also commonly precipitate IIH.<sup>14</sup> Other medications associated with IIH include:

- cyclosporine;
- cytarabine;
- nalidixic acid;
- lithium;
- minocycline;
- steroids and steroid withdrawal;
- danazol;
- nitrofurantoin;
- amiodarone;
- thyroid replacement therapy;
- human growth hormone;
- leuporelin acetate;
- desmopressin;
- oral contraceptives; and
- all-trans retinoic acid.<sup>3,4</sup>

Certain medical conditions are also known to confer a higher risk of IIH. Several studies have illustrated a link between many types of anemia and IIH.<sup>3</sup> Sickle-cell disease patients also have an increased risk of IIH.<sup>16,17</sup> The prevalence of IIH in Down syndrome is 3.4 percent, which is much higher than that found in the general pediatric population.<sup>15</sup> Turner syndrome also confers an increased risk for IIH, with or without the need for growth hormone.<sup>18,19</sup>

## Clinical Presentation

The clinical presentation of pediatric IIH is similar to that in adults. Headache is the most common symptom and is present in approximately



90 percent of patients.<sup>20</sup> There is no headache pattern that is specific for IIH. IIH may also present with no symptoms after the discovery of elevated or frankly edematous optic nerves on routine eye exam. Other symptoms include neck, shoulder or arm pain, nausea, vomiting, pulsatile tinnitus, diplopia, blurred vision and transient visual obscurations.<sup>21</sup> The diagnosis can be very challenging to make in young children who may have non-specific symptoms and cooperate poorly with the dilated fundus exam. Visual loss from IIH can also present as a visual field defect, with an increased blind spot as the most common defect (See Figure 2).<sup>22</sup> Alternatively, it may present as blurry vision from a hyperopic shift, submacular fluid extending from the edematous optic nerve, or macular choroidal folds.<sup>3</sup>

### Workup & Diagnosis

A thorough history is the first step in a proper workup when IIH is suspected; it should focus on uncovering risk factors and symptoms consistent with increased ICP. The evaluating ophthalmologist should ask direct questions specifically regarding blurry vision, transient visual obscurations, binocular horizontal diplopia and pulsatile tinnitus. A complete list of medications should complement questions to probe for underlying genetic disease, endocrine conditions or a history of anemia. A nutritional history may also be of use, particularly in adolescents whose obesity may contribute to their condition.

The neuro-ophthalmic exam should include visual acuity, pupillary evaluation for a relative afferent defect, color vision, extraocular motility, slit lamp exam, dilated fundus exam and visual fields. Either au-

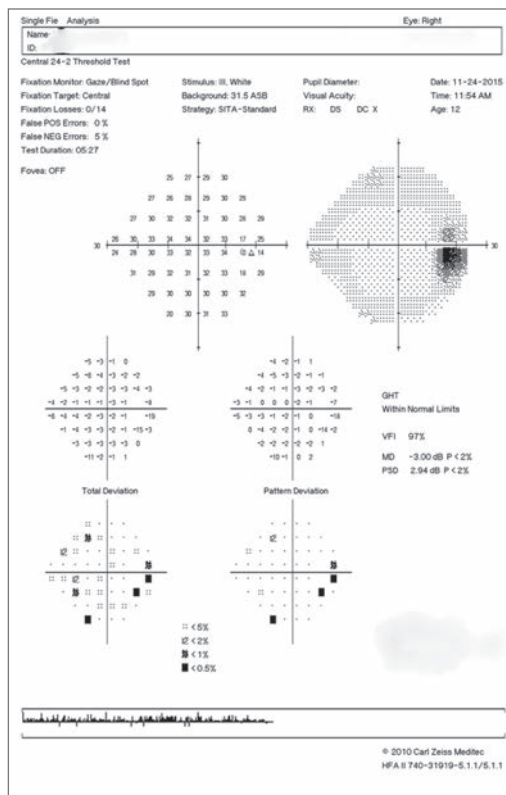


Figure 2. Humphrey visual field showing enlargement of both blind spots in a child with papilledema from IIH.

tomated visual fields or Goldmann visual fields are acceptable; however, many younger children will be unable to participate. For such patients, confrontation fields should be documented, if possible. Normative values for peripapillary nerve fiber layer thickness in children are currently unavailable; however, an OCT image should be obtained to document baseline thickness and evaluate improvement over time. If there's any doubt about whether the patient has optic nerve edema, a B-scan ultrasound should be obtained looking for optic nerve head drusen, which is a common cause of misdiagnosis.

Neuroimaging to rule out an intracranial mass should be obtained before lumbar puncture to avoid the possibility of brain herniation. The study of choice is an MRI of the brain and orbits with and without

contrast. Magnetic resonance venography should also be obtained in adults to rule out dural sinus thrombosis; this is a rare cause of increased ICP in children, however, and its utility may be limited for patients without an extenuating clinical circumstance. MRI findings associated with increased ICP include protrusion of the optic nerve head into the globe, enhancement of the optic nerve head, tortuosity of the intraorbital optic nerve, increased perioptic CSF, flattening of the posterior sclera, empty sella, cerebellar tonsillar descent, meningoceles and enlargement of Meckel's cave.<sup>3</sup>

A complete blood count should be obtained to screen for anemia. After neuroimaging, a lumbar puncture should be performed with a measurement of opening pressure. The CSF constituents must be normal, excluding other causes of increased ICP, like meningitis.

Opening pressure must be high to make the diagnosis of ICP, but this determination warrants special considerations with children. Recently, a study established a normal opening pressure of 19.6 cm H<sub>2</sub>O in children, with lower and upper limits of normal as 10.5 cm H<sub>2</sub>O and 28 cm H<sub>2</sub>O, respectively.<sup>23</sup> Recent updates to the modified Dandy criteria reflect these parameters.<sup>24</sup> The study also reported that children who received significant sedation had a higher opening pressure by 3 cm H<sub>2</sub>O on average. Since many children must be sedated to perform a lumbar puncture, this finding should lead the clinician to interpret opening pressures with caution if the child has been sedated. The sedating physician should aim to provide the minimal amount of necessary anesthetic, and the overall clinical picture should be consistent with the opening pressure before

beginning treatment.

## Treatment

Before initiating treatment, medications that are known to precipitate IIH should be discontinued, if possible. In addition, if obese, the patient and parents should be counseled that weight loss of approximately 10 percent of body weight has been shown to provide significant benefit for patients with IIH.<sup>25</sup> Medical treatments are generally aimed at decreasing CSF production by interfering with carbonic anhydrase, which is critical to its production by the choroid plexus. Acetazolamide is the most commonly used first-line agent, which has been shown to be superior to placebo and improve visual field defects from IIH.<sup>26</sup> Common side effects include gastrointestinal upset, paresthesias, malaise, nephrolithiasis, and an altered taste for carbonated beverages.<sup>3</sup> Topiramate is an anti-epileptic that also works to inhibit carbonic anhydrase and can be used as a primary or adjunct treatment for IIH. A recent study directly comparing acetazolamide to topiramate showed approximately equal efficacy.<sup>27</sup> Topiramate also promotes weight loss, which may help obese adolescents.<sup>28</sup> Furosemide can also be used as medical treatment for IIH, but may provide only a modest reduction in ICP.

When medical treatment fails, surgical treatment to reduce ICP must be considered. The most commonly performed procedure is placement of a ventriculoperitoneal or lumbo-peritoneal shunt. These procedures are able to achieve immediate reduction in ICP that may be necessary when visual field loss is severe.<sup>3</sup> Optic nerve sheath fenestration is also a viable option for surgical management of IIH, though it's not been shown to be either superior or inferior to shunt placement.<sup>29</sup> A patient with severe

headaches may benefit more from shunt placement, while patients who are otherwise poor surgical candidates may be good candidates for optic nerve sheath fenestration, which is less invasive. Recently, transverse venous sinus stenting in an attempt to increase venous outflow has been proposed as a treatment for IIH. This procedure has been reported in children, but long-term safety has not yet been established.<sup>30</sup>

Generally, the outcomes in pediatric IIH are favorable, with most children improved with only medical management. One study reported the visual outcomes of 68 children with IIH and determined that the majority of those who presented with either visual acuity or field defects had near complete recovery.<sup>31</sup>

Pediatric IIH in young children represents a unique entity and isn't necessarily associated with female sex or obesity. Older children and adolescents with the disease tend to have demographic characteristics similar to adults. Normal parameters for ICP are different for children and opening pressures can be considered normal until above 28 cm H<sub>2</sub>O. The treating clinician should be aware that sedation could significantly raise ICP and lead to a falsely positive high opening pressure. A mildly increased opening pressure should only be treated if it makes sense as part of the child's complete clinical picture. Outcomes are generally positive, and the disease can be treated either medically or surgically. **REVIEW**

*Dr. Fecarotta is in private practice.*

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# When Should You Neuroimage Your Patient?

Neurologic disease may present with symptoms that mimic glaucoma. Here's how to know when to check for trouble.

*Mark L. Moster, MD, Philadelphia*

**O**ne of the dangers any doctor faces in practice is misdiagnosis. This can lead to inappropriate treatment that allows harm to come to the patient—not to mention possibly resulting in legal action against the doctor. In fact, misdiagnosis of neurologic disease accounts for a small but significant minority of malpractice cases against ophthalmologists.

How often do glaucoma and neurologic problems overlap? Glaucoma is a common disease, which means patients with brain tumors or other neurologic diseases often have glaucoma as well. In medicine we usually try to explain all of a patient's symptoms as being caused by a single disease. If someone has headache and numbness, we don't assume he has two different diseases. But as Hickam's dictum states: "Patients can have as many diseases as they damn well please." The reality is that some patients actually do have two problems, and some glaucoma patients also have neurologic disease.

When treating glaucoma, neurologic disease can be easy to miss. In fact, if you treat glaucoma on a regular basis, sooner or later you're likely to

be fooled. That's true for a couple of reasons. First, the symptoms of many optic neuropathies can mimic those of glaucoma. Intraocular pressure can be normal or elevated in both situations, and visual field defects associated with other optic neuropathies may be identical to those associated with glaucoma.

Furthermore, cupping occurs in many types of optic neuropathy—a fact that's not well appreciated. In one study, 20 percent of optic atrophy eyes had cupping, and 6 percent of them looked typical for glaucoma.<sup>1</sup> Conditions that can cause optic disc cupping include:

- compressive optic neuropathy;
- retrobulbar neuritis;
- papillitis;
- Leber's hereditary optic neuropathy;
- autosomal dominant optic atrophy;
- infectious optic neuropathy (e.g., syphilis);
- toxic optic neuropathy (e.g., ethambutal);
- trauma;
- central retinal artery occlusion; and,

- arteritic ischemic optic neuropathy.

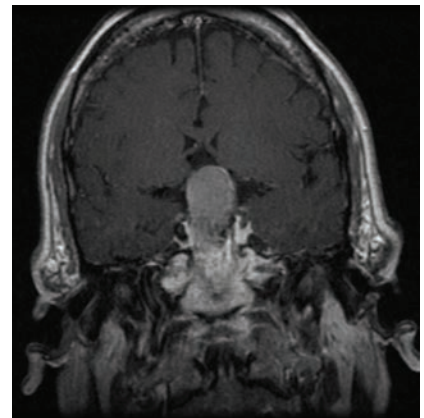
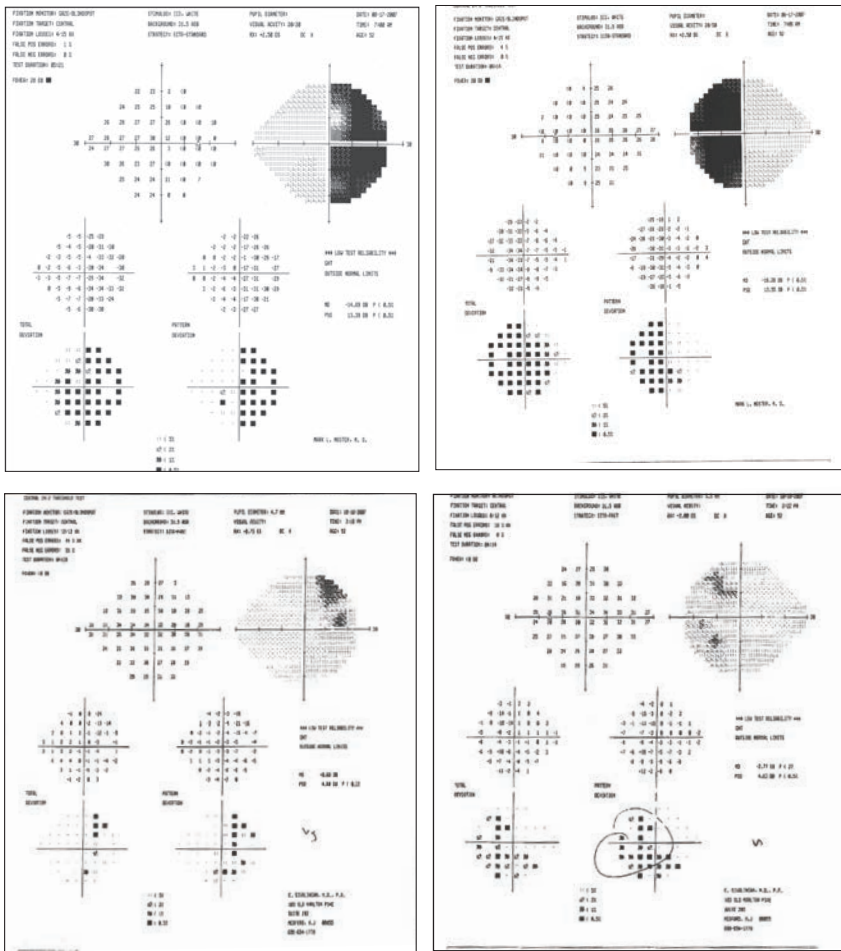
All of these can occasionally be mistaken for glaucoma and should be considered when you suspect that something other than glaucoma may be going on. It's worth noting, however, that an MRI isn't equally helpful in diagnosing everything on this list. Neuroimaging would be most helpful in making a correct diagnosis in compressive optic neuropathy and optic neuritis; other conditions listed above would require different diagnostic approaches.

Here, I'd like to discuss some of the ways you can distinguish between glaucoma and neurologic disease, with an emphasis on which signs and symptoms should make you consider performing neuroimaging of your glaucoma patient.

## Warning Signs: Visual Fields

It's important to take note when visual fields are not typical of glaucoma. Sometimes a patient who has definitely been diagnosed with glaucoma will show progression that's not typical of the disease. We've seen numerous patients with preexisting





An unusual visual field should alert you to consider a neurological problem. This patient presented with bi-temporal hemianopia (visual fields, above, left). MRI revealed a large pituitary tumor, compressing and elevating the optic chiasm (above). After surgery, the visual fields improved dramatically (left).

effect; the visual fields done six weeks postoperatively (left) show a dramatic improvement in the patient's field.

Another example: Consider the case of a 79-year old man who was being followed for pseudoexfoliation. His IOP was always in the low teens, but he had a superonasal visual field defect in the right eye which progressed over time. (*See images, next page.*) As a result, his ophthalmologist scheduled him to do a laser.

He came to us for a second opinion. I looked at his optic nerves; they didn't appear to be significantly cupped. Then I reevaluated his visual fields. The defect in the right eye did appear to be a standard glaucoma defect—it was an arcuate, superonasal defect. But the defect in his left eye was a temporal defect, which is atypical. Furthermore, it bordered on the vertical meridian, which is also atypical. Considering the two fields together, this looked like a left homonymous superior quadrantanopia, suggestive of a lesion behind the optic chiasm on the right.

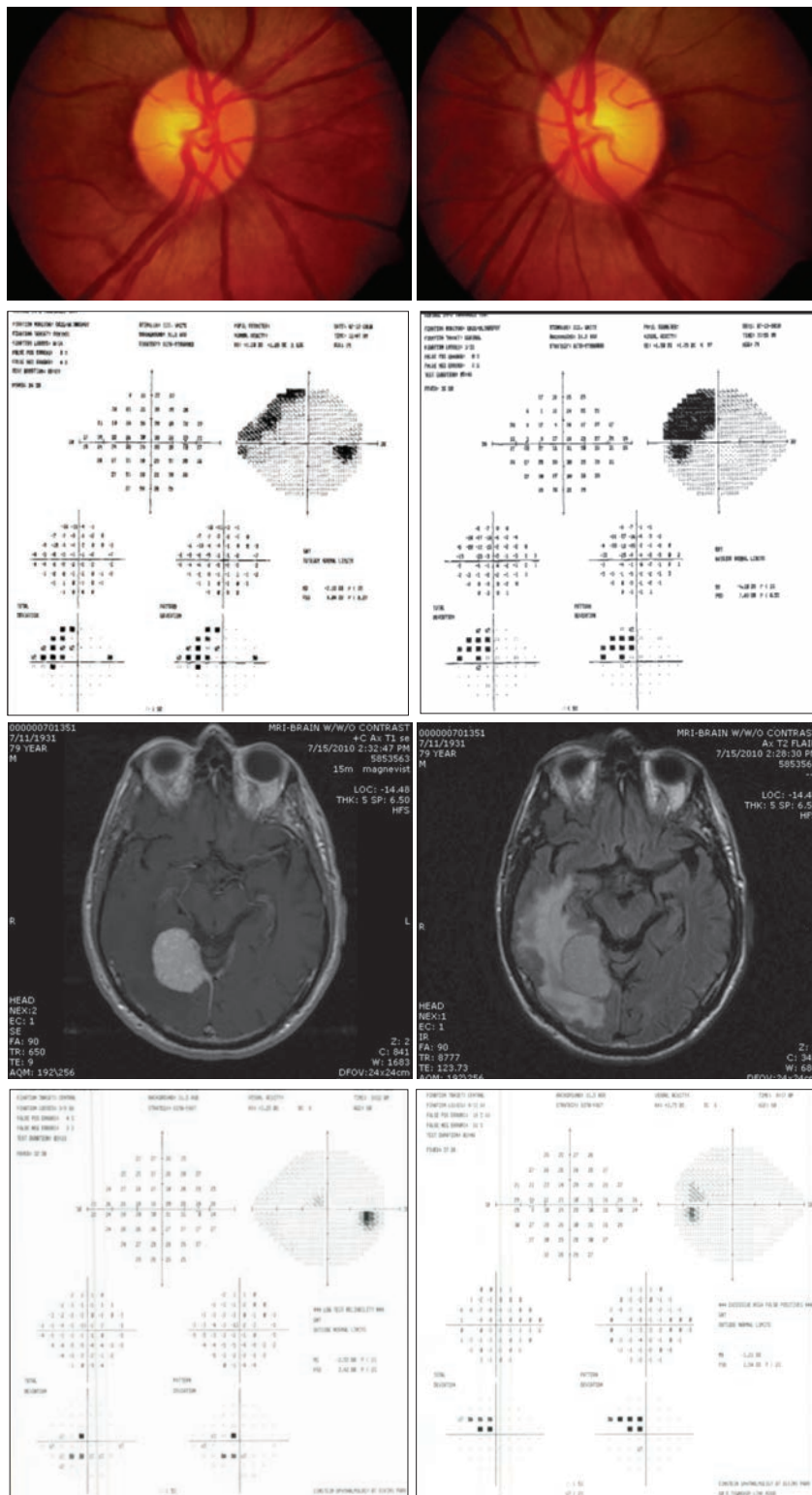
Given this evidence, we did an MRI;

glaucomatous defects develop a superior bi-temporal defect on top of the glaucomatous defect; testing revealed a lesion of the optic chiasm. Also, the rate of change may be rapid, considering the level of glaucoma control.

Although a few visual fields caused by neurologic disease may resemble glaucomatous visual fields, a field that's distinctly unusual should prompt you to consider a neurologic problem. A typical glaucomatous field might show a superior arcuate defect; but when the visual field reveals a central or cecentral scotoma; a bitemporal loss; a vertical hemianopic field loss; an inferior altitudinal defect; or visual field loss not proportional to optic disc cupping, you should consider neurologic disease. For example, a

visual field that respects the vertical meridian suggests a classic lesion of the optic chiasm. Some defects caused by a neurologic problem may resemble a glaucomatous defect, such as an inferior altitudinal defect. However, you should at least consider the possibility that such a defect could have been caused by an ischemic optic neuropathy—a lack of blood flow to the nerve.

For example, consider the visual fields shown above, from a patient with a classic bi-temporal hemianopia. Of course, this type of field is atypical for glaucoma, and in fact MRI revealed a large pituitary tumor, compressing and elevating the optic chiasm. It's worth noting that addressing the cause of the problem via surgery can have a dramatic



A 79-year old man being followed for pseudoexfoliation. His IOP remained in the low teens and his optic nerves were not significantly cupped, but he had a superonasal visual field defect in the right eye which progressed over time. MRI revealed a very large meningioma in the brain with adjacent edema. Following surgery, his vision improved dramatically.

we found a very large meningioma in the brain with adjacent edema. The patient underwent surgery, and as you can see from the visual fields at the bottom, following the surgery he experienced a dramatic improvement in his vision. (In a case like this, no matter which MIGS device you favor, you wouldn't get a great result with glaucoma surgery!)

### Warning Signs: The Optic Nerve

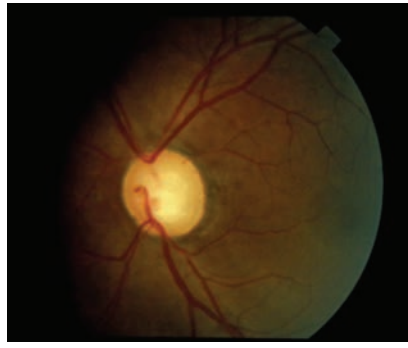
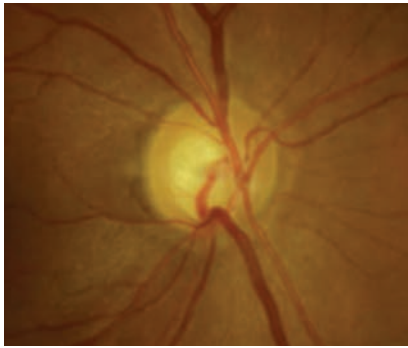
The condition of the optic nerve can provide significant clues to a neurologic problem:

- **Remember that cupping can be caused by compressive optic neuropathies.** A study conducted at Massachusetts Eye and Ear looked at the cup-to-disc ratio in patients who had unilateral compression of the visual pathway.<sup>2</sup> The cup/disc ratio on the side with the compression of the visual pathway was 0.13 greater than the cupping on the contralateral side, a direct result of the brain tu-mor. Cupping can also be caused by conditions such as multiple sclerosis or neuromyelitis optica.

- **Note the state of the patient's visual acuity relative to the cup-to-disc ratio.** Optic neuropathies are often associated with poor visual acuity despite a mild increase in cup-to-disc ratio. In contrast, in glaucoma, visual acuity is preserved until cupping is severe.

- **Note the timing of cupping.** In glaucoma, cupping of the optic nerve is seen before vision loss occurs. In neurologic disease, cupping of the optic nerve is usually seen after visual loss has begun.

- **Note the condition of the optic nerve rim.** Focal or diffuse obliteration of the rim is relatively specific for glaucoma. In contrast, pallor of the preserved rim is highly suggestive of other causes of optic neuropathy.



Focal or diffuse obliteration of the rim is relatively specific for glaucoma, while pallor of the preserved rim is highly suggestive of other causes of optic neuropathy. Above left: Focal partial obliteration of the rim inferiorly in glaucoma. Right: A patient with multiple episodes of optic neuritis. Note cupping, but also pallor of the temporal rim.

## Other Considerations

Other strategies that will help you avoid being fooled include:

- **Be extra vigilant if the patient is young.** Glaucoma tends to be less common in young people, so at least consider neurologic disease in a young person.

- **Look for symptoms often associated with neurologic disease.** These would include headache, ocular pain and ocular motility defects.

- **Note an afferent pupillary defect.** A glaucoma patient with a very asymmetric cup or asymmetric field can have a relative afferent pupillary defect (rAPD). But if you don't find an asymmetric cup or field and you see an rAPD, then you have to think neurologic.

- **Note a color vision defect.** It's very important to measure color vision. Although glaucoma causes a dyschromatopsia, it's usually mild in comparison to dyschromatopsia caused by other optic neuropathies.

- **Note any unexpected patterns on OCT scans.** OCT is often used when evaluating glaucoma patients. If you see a pattern that doesn't fit your expectations for a glaucoma patient, consider the possibility of a neurologic problem. For instance, an early binasal loss on a ganglion cell analysis suggests a compressive lesion

at the optic chiasm.<sup>3</sup>

- **In general, the more atypical the findings, the more you should consider neurologic disease.**

Neurologic cases that resemble glaucoma often present with multiple aspects that are not typical of glaucoma. Atypical findings would include an atypical medical history, an atypical exam, an atypical optic disc, a large amount of asymmetry, unexpectedly rapid progression and/or abrupt visual loss. If the history, exam, optic disc and visual fields are all close to what you would expect, you're probably dealing with glaucoma. But if more than one of those are atypical, your mental alarm should go off: The signs and symptoms you're seeing could be caused by neurologic disease.

For example, consider the case of a 29-year old man, followed as a case of unilateral glaucoma by his ophthalmologist. When I saw him, I elicited a history of pain in the right eye with progressive visual loss over a period of a few days, which is not typical for glaucoma. He then remained stable for eight months. Ironically, he'd already had a brain MRI, but it was not focused on the optic nerve and was interpreted as normal.

When I met the patient, his IOP was 8 mmHg OD and 10 mmHg OS, but his visual acuity was 20/200 in

the right eye—a pretty severe loss for glaucoma. He also had a severe color vision defect in the right eye; he correctly read only one of 13 Ishihara plates; with the left eye he correctly identified all 13. The right eye also had a 3+ afferent pupillary defect. His fundus photos revealed cupping, much greater in the right eye, but also pallor of the right rim. In short, there was a lot that would be considered atypical for a glaucoma patient.

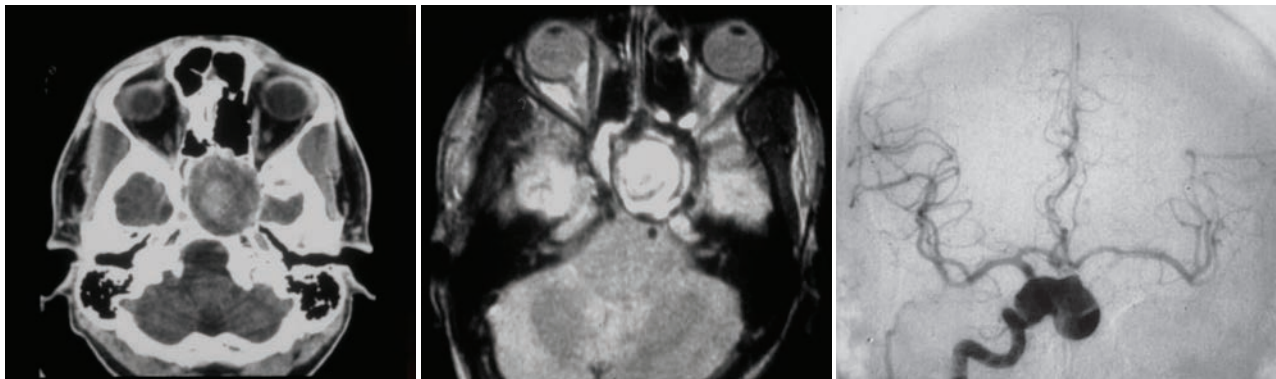
We conducted further testing. A chest X-ray revealed hilar adenopathy; the patient had an elevated angiotensin converting enzyme (ACE) level of 100; and bronchoscopy revealed noncaseating granulomas. It became clear that he was suffering from sarcoidosis with optic neuropathy; he actually didn't have glaucoma at all. Although we didn't redo the MRI scan, had the first scan been focused on the orbit, it most likely would have revealed that the optic nerve was inflamed by the sarcoidosis.

## Performing Neuroimaging

What kind of tests should you do for neuroimaging? We prefer an MRI of the brain and orbit. A CT scan is a good second choice if an MRI is contraindicated. In either case, it's crucial to communicate with the radiologist to make sure you're getting the proper scan of the proper area. You don't want to end up with a brain MRI without contrast that doesn't show the visual pathway well; you could easily miss the lesion you're looking for.

There's been some debate regarding neuroimaging of patients with typical normal-tension glaucoma. One way to address the possibility that some of these patients could have a neurologic problem would be to neuroimage all of them. However, this would be a major expense and inconvenience, and





This patient presented with slowly progressive visual loss in the left eye. Exam showed unilateral decreased visual acuity, relative APD, dyschromatopsia and a pale, cupped optic disc. CT scan (left) and MRI (middle) show a mass compressing the left optic nerve. A catheter angiogram (right) shows the lesion to be a large aneurysm coming off the right internal carotid artery.

published findings on the value of such a protocol have been mixed. In one study by Ike Ahmed, MD, 62 patients with newly diagnosed typical normal-tension glaucoma underwent neuroimaging; four of them (6.5 percent) had compressive lesions (two pituitary tumors, one meningioma and one arachnoid cyst).<sup>4</sup> However, other studies have not found any lesions. A 1998 study involving 52 eyes of 29 normal-tension glaucoma patients found no compressive lesions;<sup>5</sup> and a 2010 survey of 68 normal-tension glaucoma patients who had undergone CT scans and carotid Doppler scans revealed no other lesions.<sup>6</sup>

The reason for the discrepancy between these studies isn't clear, but given the practical difficulties of neuroimaging so many individuals, the evidence probably doesn't support neuroimaging all normal-tension glaucoma patients. On the other hand, when a patient presents with the kind of atypical findings we've been discussing in this article, neuroimaging that patient makes perfect sense.

### Taking the Hint

Misdiagnosing neurologic disease can have profound consequences. However, sometimes it requires

a leap of thinking to consider that unexplained vision loss may be the result of a neurologic problem. A glaucoma specialist I know had a patient who had been diagnosed with glaucoma 30 years earlier. About a year before I saw him he suffered dramatic vision loss, eventually reaching no light perception in one eye. He'd undergone an MRI 30 years earlier, and no problem had been detected; in addition, his recent visual field defects didn't immediately suggest a neurological problem. For that reason, a retinal problem was the first possibility they considered.

As it turned out, retinal examination didn't reveal any potential cause. The patient was also developing cataracts, so those were removed, but no improvement followed. The glaucoma specialist began to suspect that the patient was faking! Finally the patient was sent to our office, and we discovered a large pituitary adenoma. Once the adenoma was surgically removed, the patient's vision returned to baseline.

The moral of the story is: When a glaucoma patient loses vision out of proportion to what you expect given the patient's course or pressure, you need to consider other possibilities—including neurologic disease.

So, how do you decide when neuroimaging makes sense? The

guiding principle should be taking note when the signs or symptoms are not what you'd expect. Is the patient getting worse for no apparent reason? If the pressure is 25 mmHg and it should be 10 and the patient is getting worse, you're probably dealing with glaucoma. But if the pressure is 10 mmHg and it's been 10 all along, and suddenly a new, different defect appears, you need to consider the possibility of a neurologic problem and consider neuroimaging the patient. **REVIEW**

*Dr. Moster is a professor of neurology and ophthalmology at Thomas Jefferson University, and director of the neuro-ophthalmology fellowship at Wills Eye Hospital, in Philadelphia. He has no financial conflicts relating to anything discussed in this article.*

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# Ocular Trauma: Then and Now

A look at the full range of possible causes of trauma, as well as ways in which the eye can help diagnose other kinds of injury.

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

**A**fter nearly three decades of Therapeutic Topics we've covered a variety of topics, and naturally, everyone has their favorites. One of the most interesting and informative ones from our perspective comes from back in December of 2004, when we wrote a piece called "Ocular Trauma Never Takes a Holiday." In it we described the ophthalmic pitfalls associated with holiday-related activities, from firecrackers in the face to champagne corks in the eye. While as a year-end piece it was a bit tongue-in-cheek, it nonetheless highlighted clinical details of acute ocular trauma and demonstrated that the eyes provide a unique window into the physical and mental status of our patients. This month we reprise that topic, with bits of the old and a focus on important new findings on ocular trauma.

## The Gamut of Trauma

Following are the most common forms of ocular trauma patients experience:

- **Foreign bodies.** For some, the term ocular trauma is synonymous with foreign bodies, an endless list of

fragments, shards or other projectiles that somehow find their way into the globe or accessory tissues of the eye.<sup>1</sup> Workplace injuries account for many of these incidents, despite repeated reminders to use proper safety eye-wear. When the objects in question are localized outside the visual axis and/or do not penetrate beyond the cornea, the prognosis is good. One study reported that resolution of an epithelial defect in such cases is typically complete within five days, and the risk of complications such as infectious keratitis is less than 2 percent.<sup>2</sup> This might seem like a small number, but it's worth remembering that eye trauma is very common: The U.S. Eye Injury Registry reports that

there are over 2.4 million ocular injuries annually,<sup>3</sup> meaning that a 2-percent rate of complications equates to 24,000 people each year with vision-threatening trauma.

Penetration of foreign bodies through the anterior segment represents a serious, vision-threatening event. Key in these situations is removal of the foreign body, as the risk of endophthalmitis increases more than tenfold when the object remains in the eye; this is especially true when dealing with contaminated, organic or toxic foreign objects.<sup>4,5</sup> Although the slit lamp is typically the most readily accessible tool for this task, it's useful to apply CT imaging if the search is initially unsuccessful.

- **Non-contact trauma.** In some cases, ocular trauma can occur without direct physical contact. Consider, for example, the recent solar eclipse that streaked its way across the United States in August 2017. It's estimated that as little as five to 10 seconds of direct exposure to the retina can cause noticeable visual impairment. Case studies have reported a range of results: In some, retinal damage resolved within six months, while in



Light damage from staring at the sun, such as during the recent solar eclipse, is an example of non-contact eye injury.



others there were more lasting effects, even for those who claimed to just look “briefly” at the obstructed sun.<sup>6,7</sup> One report suggested that solar exposure could also disrupt the tear film.<sup>8</sup> Several studies have followed those with retinal damage over time; a Swedish study reported that of 15 patients initially identified as having foveal damage from eclipse-watching, all had central scotomas at one-year follow-up.<sup>7</sup> It’s clear from these older reports, as well as the recent eclipse, that the message of ocular safety during these celestial events doesn’t seem to get through to everyone.

• **Chemical burns.** No discussion of ocular trauma would be complete without mention of the potential damage inflicted by chemical exposure. The exposed surface of the cornea is one of the most sensitive tissues of the body, and the natural defense mechanisms of lids and tear film can exacerbate damage from a splash of alkali or acid by spreading the caustic agent over the entire ocular surface. Foreign bodies and chemical spills comprise the overwhelming majority of ocular traumas, but they are not created equal: Chemically-mediated trauma often takes a bigger toll, and involves more prolonged, more-invasive therapy and recovery than foreign-body injury.<sup>9,10</sup>

In a moderate to severe chemical exposure there is typically significant damage to the corneal epithelial layer, and often to the apparatus for production and maintenance of the tear film (goblet cells, meibomian glands). Chronic dry eye is a common sequela to corneal chemical burns. Follow-up care for an initial traumatic event will likely include medical management to allow for epithelial healing. Serum drops, limbal grafts or amniotic transplant procedures may be required in cases where epithelial and or limbal damage is significant.<sup>9-11</sup> A recent retrospective study compared three general strategies in a total of 55



Besides suffering trauma itself, the eye can also warn of trauma elsewhere in the body. For example, in addition to such symptoms as vomiting, slurred speech and disorientation, dilated pupils of unequal size is a sign of a concussion.

patients with stage III, IV or V alkali burns. One group received traditional care, one received umbilical cord serum drops in addition to traditional care, and the third group underwent amniotic membrane transplant. The study followed measures such as time to re-epithelialization, epithelial defect diameter and defect area, corneal clarity, tear breakup time, Schirmer’s test and best-corrected vision. Both supplementary intervention groups showed a decrease in time to heal, as well as improvements in TBUT and Schirmer’s score when compared to traditional treatment. The major difference between the two is that the use of drops has a measure of safety in that it does not involve an additional surgical procedure.<sup>11</sup>

## Detecting Traumatic Events

The eye is uniquely susceptible to all types of trauma, and conversely, the eyes can exhibit and report on

trauma that extends throughout the visual system. Two examples of such conditions are traumatic brain injury (TBI) and concussion, both of which have become a focus of greater interest in recent years. The extended length of American military conflicts, as well as the nature of those operations, has resulted in large numbers of veterans experiencing some degree of TBI. Recent estimates suggest that 10 to 15 percent of the 2.4 million servicemen and -women who have served in Afghanistan or in Iraq experienced some form of TBI.<sup>12</sup> While the majority of these are concussion or concussion-like syndromes, the spectrum of trauma is diverse and presents a significant diagnostic and therapeutic challenge.<sup>12,13</sup> Concussion risk in contact sports such as football or boxing has recently been brought to light by stories of retired athletes who suffered with a repeated-concussion form of TBI, and reports of league and sports officials attempt-

## Therapeutic Brief: Gene Therapy Completes Phase III

In August, Stephen Russell, MD, of the University of Iowa, and Jean Bennett, MD, of the University of Pennsylvania, and their co-workers completed the first ever controlled, randomized, Phase III trial of a gene therapy for inherited retinal disease using voretigene neparovvec (Spark Therapeutics, which also provided funding for the trial).<sup>1</sup>

In the study, 29 individuals with RPE65 gene mutations, which result in retinal dystrophy, were randomized to treatment (n: 20) or control. At one year, the mean change in bilateral multi-luminance mobility testing score for the intervention group was 1.6 light levels better than controls ( $p=0.0013$ ). Thirteen of 20 treatment participants passed MLMT at the lowest luminance level tested (1 lux), vs. none of the control participants, the maximum possible improvement. Researchers say there were no product-related adverse events.

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ing to downplay the risks of repeated head trauma.

Visual function disruption associated with TBI is variable, and to some extent depends upon the nature of the precipitating traumatic event. Most TBI patients report vision problems according to one study.<sup>12</sup> Approximately half of the patients complain about problems reading. Light sensitivity, saccadic dysfunction, accommodative dysfunction and convergence insufficiency have been reported in 60 to 85 percent of patients. Strabismus, pursuit abnormalities, fixation defects and visual field defects were also common visual findings.

Several groups have used these characteristics to aid in the development of reliable diagnostic criteria.<sup>14</sup> Ocular metrics such as tracking, response latency and response acceleration can be used to assess the severity and the characteristics of patients' underlying sensorimotor impairment, even in cases where the defects are mild enough that the patients don't recognize them as TBI. The goal is to use these types of tests to monitor progression of the trauma or as a means to assess potential therapeutic interventions. Concussion and TBI represent a spectrum of traumatic head injury, and many of the symptoms associated with concussions, such as light sensitivity, anisocoria, headache and confused mental status are shared by the two diagnoses. In most organized sports a standardized protocol is given to athletes to provide a baseline for comparison in the event of subsequent head trauma. Recently, there's been a push to incorporate more visual components into this protocol, as visual functions represent an integration of sensory and motor activity.<sup>15</sup> For example, pupillary responses are among the first reflexes tested when a patient is suspected of having sustained a concussion.

In developing programs to treat and to prevent concussion injury, it's

important to be aware that the constellation of headaches, light sensitivity and/or difficulty reading in an otherwise healthy, active young adult may suggest a possible history of undiagnosed concussion.

The newest evidence in this field suggests that trauma is cumulative and can occur without detectable symptoms. Our understanding of the processes of TBI and concussion has a long way to go, but it may be that visual metrics will lead us to better diagnostics for both. In so doing, they could also ultimately provide the clinical endpoints we will need to develop effective therapies.

*It's important to be aware that the constellation of headaches, light sensitivity and/or difficulty reading in an otherwise healthy, active young adult may suggest a history of undiagnosed concussion.*

As a closing thought, one of the things about trauma in general is that common sense tells us that the real therapeutic cure for these problems is prevention, whether it's safety glasses, eclipse glasses, improved football helmets or more persuasive diplomacy. Yet, we never seem to achieve that perfect safety record.

One area where visual testing improvements may have an impact on reducing trauma is in automobile safety. We all have or know of older

friends or family members who have reached the age where their visual function might not be up to the task of driving the highways. An improved visual test called the Useful Field of View test provides a more integrated assessment of the visual tasks such as tracking, attention and acuity needed for safe driving.<sup>16</sup> If both young and old would take the test, perhaps there would be a little less trauma in the world. **REVIEW**

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# The Pros and Cons of Heads-up Surgery

The future of this technology holds promise as long as new innovations are critically evaluated, these surgeons say.

*Murtaza K. Adam, MD, Denver, and Allen C. Ho, MD, Philadelphia*

**G**iven the lack of tactile feedback and the microscopic scale of the surgical field, visualization is one of the most important aspects of performing vitreoretinal surgery. Until recently, our only instrument for intraocular visualization was a microscope using classical optics, with its associated limitations in field of view, color, contrast and sharpness. Now, with advances in digital displays and image processing, we have the ability to augment the visualization of our surgical field in real time. In this article, we'll share our initial impressions of the TrueVision 3D visualization system as part of an Alcon-sponsored, prospective trial we've initiated at Wills Eye Hospital in Philadelphia.

## The Technology Evolves

In 2008, TrueVision Systems first entered the market with a three-dimensional, heads-up ophthalmic surgical visualization system. Using a high-definition display, a camera connected to a traditional surgical microscope, and passive 3-D glasses, their principal idea was to free the ophthalmic surgeon from the constraints of

the operating microscope (*Figure 1*). Some anterior segment surgeons immediately began using the technology, since heads-up visualization allows for a seamless overlay of preoperative and intraoperative data, such as toric overlays and phacoemulsification metrics.

Sony also entered the market in 2013 with its own version of a 3-D heads-up visualization system for neurosurgery and ophthalmology, but its impact upon the vitreoretinal market

has been less significant. This is likely due in part to the partnership forged by Alcon and TrueVision in 2016 to create NGENUITY, a visualization platform specifically created for digitally assisted vitreoretinal surgery.

Over the intervening years since the system's introduction, TrueVision/Alcon have made several improvements to the system, including a fifth-generation, high-dynamic-range 3-D camera, integration of a 55-inch, 4K OLED TV, and much-improved la-



Figure 1. 3D heads-up display with five observers watching Murtaza Adam, MD, operate. The setup consists of an ICM 5 high-dynamic-range camera connected to an operating microscope and a 4K OLED display placed approximately a meter away from the surgeon.



tency (i.e., the perceived delay between when you make an action and when you see it displayed). With any medical innovation, however, all potential advantages over the current paradigm are undermined by questions of clinical utility and economics. Does performing 3-D heads-up vitreoretinal surgery result in better visual outcomes? Will there be a lower complication rate? Will surgery be more efficient, resulting in reduced operative time? Will the surgery be more ergonomically comfortable? In a medical system with limited resources, these are important questions that need to be answered.

### A Dearth of Data

At this time, few scientific studies have attempted to answer the questions listed above. In 2015, Claus Eckardt, MD, and Erica Guerreiro Paulo, MD, published the first peer-reviewed study comparing the traditional microscope to the TrueVision 3D heads-up platform.<sup>1</sup> The authors prospectively and systematically evaluated the performance of 20 volunteers carrying out various tasks (arranging small objects with forceps, tying sutures, etc.) using a standard operating scope and the TrueVision system. Although the authors found that the resolution of the traditional microscope was twice that of the digital display, they didn't feel that this was a significant obstacle, and they reported no differences in performance. More than 90 percent of the study participants preferred the ergonomics of the heads-up technique.

In the same publication by Drs. Eckardt and Paulo, a retrospective analysis of 43 macular hole repairs performed using the TrueVision system revealed a primary hole closure rate of 97.7 percent, which was comparable to their success rate with a traditional microscope. The authors also performed a preliminary explo-

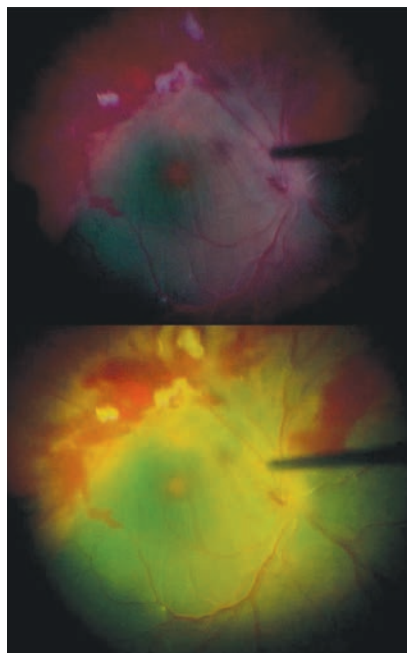


Figure 2. Indocyanine green dye-assisted chromovitrectomy in a patient with proliferative diabetic retinopathy before (top) and after (bottom) activation of a digital filter to enhance visualization of the internal limiting membrane.

ration of amplifying digital gain (the ability of a sensor to amplify the ambient light in order to provide an image without the need for brighter illumination) to minimize the need for endoillumination during vitreoretinal procedures and its associated risk of phototoxicity.

Building upon this work, two additional publications, including one by our group at Wills, more rigorously examined the power of digital amplification in reducing endoillumination requirements during vitreoretinal surgery.<sup>2,3</sup> Both small case series reported safely performing a variety of vitreoretinal cases with endoillumination levels at less than 5 percent of maximum output, a task that would be extremely difficult with a traditional scope.

This limited body of work represents preliminary attempts to demonstrate the potential of 3-D heads-up surgery and identify areas in need of

improvement. At Wills Eye Hospital, our investigator-initiated, prospective, randomized, controlled trial is currently under way to explore these same areas of interest. Our study aims to compare detailed intraoperative metrics and postoperative outcomes of patients with macular holes, epiretinal membranes and retinal detachments, randomized to undergo surgery with a traditional operating microscope or the NGENUITY system. Our hope is that other groups will perform similar objective and quantitative analyses to provide a realistic assessment of the system's ability to affect patient care, and identify ways to maximize its potential.

### A Dash of Subjectivity

Our experience with 3D heads-up vitreoretinal surgery over the past year has been largely positive. From a subjective standpoint, after we began using the the NGENUITY system, we've found that our support staff has become more engaged and attentive, because anyone wearing passive 3-D glasses in the OR shares the surgeon's 4K, stereoscopic OLED view. This shared viewing ability has helped many on the OR staff, as well as medical students and residents, to have a better understanding of the methods and goals of surgery. When we use a standard operating microscope, the attending and fellow occupy the only oculars available, forcing observers to watch the 2-D monitor located away from the surgical field. In contrast, observation with the much larger heads-up display is limited only by the number of 3-D glasses available and observers can stand immediately behind the surgeon, allowing for a more intimate teaching experience (See Figure 1, p. 53).

The 3D heads-up platform performs well in macular cases and diabetic tractional detachments. The field of view is broad and stereopsis

is excellent, even with high magnification. This allows for wide, confident peeling with excellent peripheral awareness. Additionally, real-time digital filtering can be used to highlight internal limiting staining achieved during chromovitrectomy (Figure 2) and digital gain manipulation can significantly reduce endoillumination requirements (Figure 3). Integration of intraoperative optical coherence tomography also works seamlessly with the heads-up system and provides high-resolution scans of macular anatomy (Figure 3). In diabetic tractional detachments, the movement of a peripherally detached retina when peeling posterior fibrovascular tissue is easily detected, giving the surgeon more confidence in his or her ability to avoid creating iatrogenic breaks (Figure 4).

Primary and complex retinal detachment repairs are intuitive with the 3-D heads-up platform. However, we've encountered occasional issues with decreased peripheral acuity and washed-out images when performing peripheral laser.

The traditional operating scope has the advantage of using the surgeon's pupils and lens (with associated accommodation) as part of the optical system to balance image exposure and facilitate a clear peripheral examination. With 3-D heads-up surgery, however, the final pathway for light is the high-dynamic-range camera mounted on the operating microscope, which has limits to its exposure modulation and depth of field. In high myopes, the heads-up system appears less forgiving than the traditional scope and refocusing at the conclusion of the case for peripheral inspection reduces the risk of missing small tears.

The focus control with our current setup is quite sensitive and refocusing in the middle of a case can be cumbersome. We've found that parfocusing at the beginning of all 3-D cases and markedly decreasing the light in-

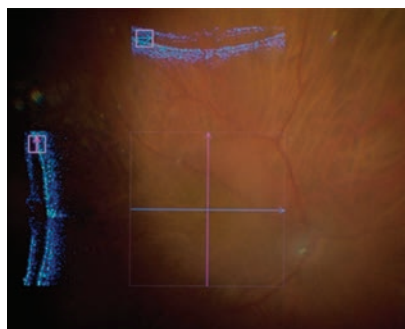


Figure 3. Intraoperative optical coherence tomography of a small macular hole following epiretinal membrane and internal limiting membrane peel. The entire case was performed with 5-percent endoillumination to minimize the risk of macular phototoxicity.

tensity when performing peripheral laser with scleral depression can help minimize these issues.

Overall, we have found working in the vitreous cavity to feel quite natural and comparable to the standard operating microscope. Digital image latency isn't an issue when performing vitreoretinal surgery, since movements within the posterior segment are typically slower than maneuvers performed anteriorly. However, when working on the anterior segment, the digital latency becomes more evident and the surgeon's hands should slightly slow to compensate for this. Also, the field of view of the anterior segment is smaller with the heads-up

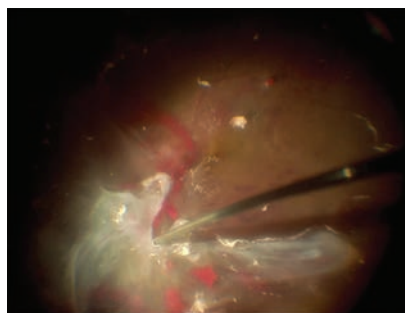


Figure 4. High resolution maintained with a wide field of view during dissection of preretinal fibrovascular plaques in a patient with a macula-involving diabetic tractional detachment.

platform compared to the standard operating microscope. These factors lead to slightly awkward corneal, conjunctival and scleral suturing, especially when working with long sutures.

## Looking Ahead

Significant improvements to the latest-generation platform are already on the way, including real-time integration of vitrectomy machine parameters, a streamlined purely digital microscope, the addition of digital filters, and the ability to overlay preoperative and intraoperative data on the surgical field. As each advance in heads-up surgery arrives, however, it's imperative that we clinicians participate in guiding its evolution to improve outcomes and maximize safety. Our patients are depending on us. [REVIEW](#)

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# Options for Small-Incision Brow Lifts

In some patients, a traditional brow lift may not be necessary; a less-invasive option may yield the results they need.

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**T**he old adage, “Use the right tool for the job,” also applies to surgical procedures. For patients in whom brow ptosis is a main cause of, or significant contributing factor to, their complaints of drooping lids, you may not need to subject them to the expense and significant morbidity of a formal brow lift using a coronal or endoscopic approach. Sometimes, in patients with mild or moderate brow ptosis, the right procedure for the job is a less-invasive option that can be performed through a small incision and doesn’t require undermining large amounts of tissue, limiting morbidity and making it more palatable to patients. In this article, we’ll detail such procedures, and outline their pros and cons. Note that these procedures shouldn’t be considered overall replacements for a traditional brow lift, but they can still be used successfully in a good number of these sorts of patients.

## The Patient’s Complaint

Evaluation of eyelid and brow position is an important part of an ophthalmologist’s external exam. The tis-

sues of the eyebrow and eyelid are functionally linked, and changes in the position of one will affect the form and function of the other. Patients will often have concerns about their eyelids drooping, and it’s only through a careful exam that one can determine whether that complaint is caused by blepharoptosis, dermatochalasis, brow ptosis or a combination of these factors. While ophthalmologists often take note of ptosis and dermatochalasis as part of a general eye exam, brow ptosis is more likely to be overlooked.

The relationship between eyelid and brow position is complex, and it’s clear that the eyelid and brow are structurally and functionally connected. So, just as when you’re evaluating a patient’s complaint, remember that performing surgery on one without consideration for the effects on the other is a recipe for an unsatisfied patient. A review of the literature suggests that surgery to correct blepharoptosis results in brow descent,<sup>1-3</sup> and how significant this change will be to the patient functionally or aesthetically will differ in each case. Blepharoplasty alone can also lead to a significant drop in brow position,

though studies addressing this topic have reached mixed conclusions.<sup>1,4-8</sup>

If your exam determines that the patient has mild to moderate brow ptosis, and you’d like to avoid issues associated with formal brow lifts, consider the following options.

## Direct Brow Lift

One option for these brow ptosis patients is a direct, or transcutaneous, brow lift.<sup>9,10</sup> The advantages of this procedure are that it’s relatively simple to perform, gives the surgeon good control of the amount of lift and has the ability to address medial brow ptosis. The main drawback of this procedure is the resultant scar above the brow. In our experience, a lateral brow lift can be achieved with a reasonable scar, although when the incision is carried more medially the scar become significantly more apparent.

When using this procedure to elevate the male brow it’s important to pay particular attention to the contour, taking care to preserve a flatter brow and avoid a feminizing, highly arched brow. Several techniques have been described to try and improve



the appearance of this scar, including beveling the incision, sutured lifting of the orbicularis to relieve tension, and postoperative scar treatments.<sup>11,12</sup> Meticulous surgical techniques can improve the appearance of the scar, but for a portion of patients any scar can be cosmetically unacceptable. Additionally, there is also the possibility of significant paresthesia of the forehead, especially if the supraorbital nerve and vessels are not meticulously protected against damage during the procedure.

### External Browpexy

This technique, first described in 2012 by Beverly Hills, Calif., surgeon Guy Massry, MD,<sup>13</sup> provides a moderate lateral brow lift through a small incision.

To perform external browpexy, the surgeon marks the point of desired brow elevation near the junction of the tail and body of the brow, then makes a small, 8-mm incision just superior to the brow cilia. Dissection is carried through the skin and subcutaneous tissues close to the level of the periosteum. The dissection is carried superiorly to the level of desired fixation. The surgeon then secures the subcutaneous orbicularis and the brow fat pad to the periosteum at the desired level of fixation with a permanent suture and closes the incision. This technique results in a small and usually cosmetically acceptable scar. A quantitative study showed the external browpexy can provide approximately 3 mm of lift to the lateral brow.<sup>14</sup> Complications of this procedure include pain and edema at the suture site. This pain usu-

ally resolves over the course of about a month, but should be discussed with the patient preoperatively.

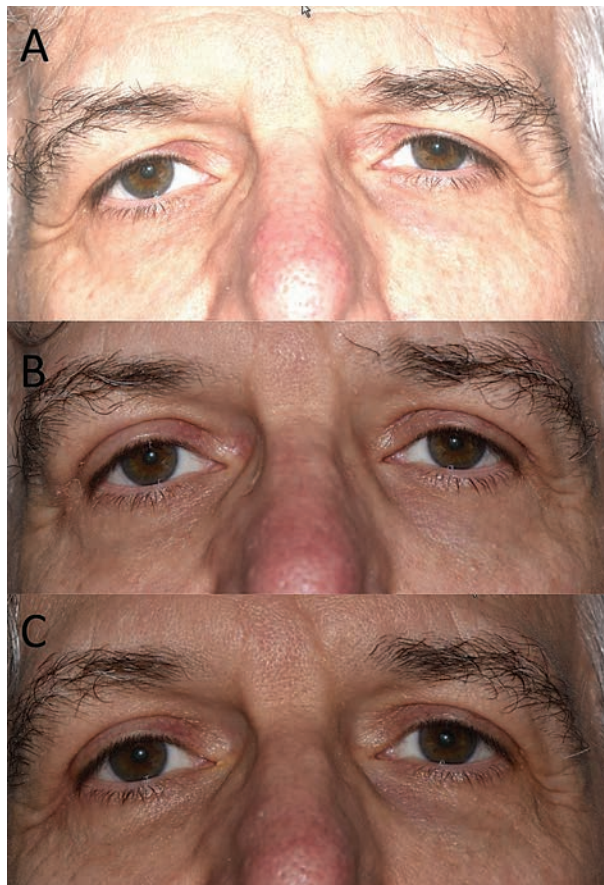
The procedures we've discussed so far involve an incision superior to the brow. While this type of incision results in some amount of scarring, it has the advantage of making it possible to perform these brow-lifting procedures in isolation from other periorbital procedures. This allows for correction of brow ptosis or asymmetry without making an upper-eyelid incision. The remainder of the techniques that we will discuss are most appropriately performed

concurrently with blepharoplasty and take advantage of the standard blepharoplasty incision.

### Internal Browpexy

The internal browpexy is an effective procedure that can provide a moderate lift to the lateral brow. It is not the ideal procedure for patients with severe brow ptosis or those with significant medial brow ptosis. The main advantage of this procedure is that it's performed through the blepharoplasty incision, which usually heals very well with minimal scarring. It's important to note that the browpexy will elevate the brow to a more appropriate position, causing a resultant stretching of the upper eyelid skin and less redundancy of the upper eyelid skin. Care must be taken to avoid removing too much skin from eyelids that are having a concurrent brow-lifting procedure, in order to avoid lagophthalmos and accompanying corneal complications.

In the preoperative area, it's helpful to mark the point of desired elevation near the bottom of the brow cilia at the junction of the tail and body of the brow with the patient in an upright position. Once the blepharoplasty incision is made, the dissection is carried superiorly over the orbital rim in a pre-periosteal plane to a level 15 to 20 mm above the orbital rim. The surgeon then places a suture at full thickness through the skin and subcutaneous tissues at the mark made preoperatively; this pass serves as a marking suture. He or she then passes the suture through the periosteum ap-



Blepharoplasty and external browpexy, pre- and postop. Preoperative photo (A): Notice significant lateral brow ptosis and dermatochalasis. Postoperative photo, two weeks after blepharoplasty and external browpexy (B): Notice some redness in the area of the incisions over the lateral brow. Postoperative photo, two months after surgery (C): Notice the improved appearance of the external browpexy incisions.

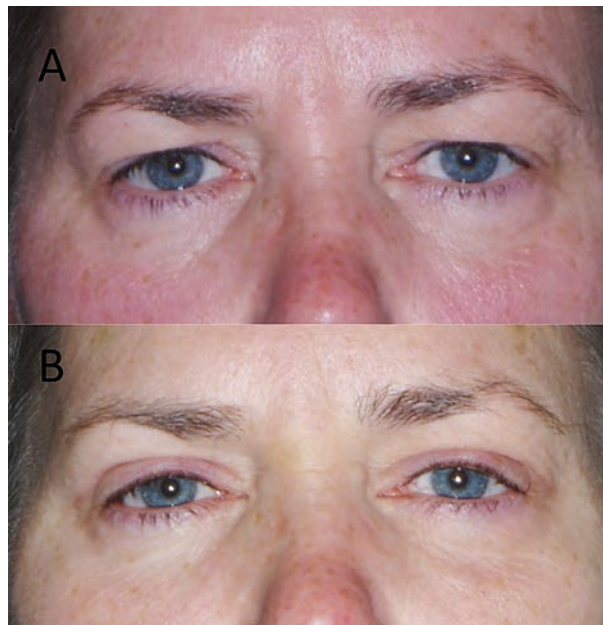
proximately 10 mm above the orbital rim and again through the subcutaneous tissues adjacent to the previously placed marking suture. The marking suture is then pulled until the free end of the suture pulls through the dissection flap and the subcutaneous tissues are secured to the periosteum as the suture is tied. Multiple variations on this technique have been published.<sup>15,16</sup> Quantitative studies suggest that this technique provides somewhere between 1 to 2 mm of lift to the lateral brow.<sup>14,7</sup>

Complications of this procedure include pain at the suture site, which usually resolves over a few weeks. There is also the possibility of creating an unsightly dimple in the brow skin if the browpexy suture is passed too superficially.

### Brassiere Suture

The goal of this procedure is to use the orbicularis to suspend the brow fat pad and create a barrier to the descent of the brow tissues. As a result, this procedure can provide volumization and aesthetically pleasing anterior projection of the lateral brow and help to preserve the contour of the lateral superior sulcus. For patients who complain of skin covering their lateral tarsal plate, this procedure can produce an excellent aesthetic result.

Like the internal browpexy, this procedure also takes advantage of a previously made blepharoplasty incision. After the blepharoplasty incision has been made and the skin excised, the surgeon incises the orbicularis and divides it into roughly equal-sized upper and lower portions. Dissection under the superior portion of the orbicularis is carried



Preoperative photo before blepharoplasty and brassiere suture (A) demonstrates the upper eyelid skin fold obscuring the central and lateral tarsal plate. Postop (B), note the elevated brow and preserved lateral tarsal show.

to the level of the orbital rim. An absorbable suture is then used to secure the cut end of the upper orbicularis to the underlying arcus marginalis, effectively creating a sling or hammock for the brow tissues above. You can place several sutures along the lateral rim. The incision is then closed by standard techniques. This technique and several variations have been previously described<sup>17-19</sup> and, though it can provide a lift for the brow fat pad and improved brow volume at the level of the orbital rim, in our hands it doesn't provide a significant lift to the overall brow. Therefore, patients with more significant brow ptosis would likely be better served by a different procedure.

Small-incision brow-lifting techniques such as those discussed here provide good, minimally invasive ways to address brow ptosis. A variety of available techniques allow for personalization of the surgical approach to each patient, depending on his or her needs and concerns. **REVIEW**

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# Glaucoma Screening in High-Risk Populations

**R**esearchers from Johns Hopkins University, Baltimore, conducted a one-year study to develop, implement and evaluate a replicable community-based screening intervention with the hope of improving glaucoma and other eye-disease detection and follow-up care in high-risk populations in the United States.

This prospective study is ongoing, but researchers released the one-year findings. The study focuses on African Americans over 50 years of age at multiple inner-city community sites in Baltimore. The screening examination uses a sequential referral approach and assesses presenting visual acuity, best-corrected VA, digital fundus imaging, visual field testing and measurement of intraocular pressure.

Of the 901 individuals screened between January 2015 and October 2015, subjects were mostly African Americans (94.9 percent) with a mean age of 64.3 years. Among them, 356 participants (39.5 percent) were referred for a definitive eye examination, and 107 (11.9 percent) required prescription glasses.

The most common reasons for referral were an ungradable fundus image (39.3 percent of those referred), best-corrected VA less than 20/40 (14.6 percent), and ungradable autorefraction (11.8 percent). Among those referred for definitive examination, 153 people (43 percent) attended their scheduled

examination. The most common diagnoses at the definitive examination were glaucoma and cataract (51 and 40 percent, respectively).

After one year of the ongoing study, a large proportion of individuals screened required ophthalmic services. To reach and encourage these individuals to attend screenings and follow-up examinations, researchers say that programs could develop innovative strategies and approaches.

*Am J Ophthalmol* 2017;180:18-28.  
Zhao D, Guallar E, Gajwani P, et al.

## Classification of Fluorescein Breakup Patterns

**I**n a cross-sectional study, researchers from Kyoto, Japan, investigated the relationship between fluorescein breakup patterns and clinical manifestations in dry-eye cases.

Researchers looked at 106 eyes of 106 subjects (19 male, 87 female; mean age: 64.2 years). FBUPs were categorized into one of the following five types: area (AB, n=19); spot (SB, n=22); line (LB, n=24); dimple (DB, n=19); and random (RB, n=22 eyes). They also examined dry-eye-related symptoms using the visual analog scale (100 mm=maximum); tear meniscus radius; tear film lipid layer interference grade (grades 1–5, 1=best) and spread grade (grades 1–4, 1=best); tear film noninvasive breakup time; fluorescein breakup time; corneal epithelial dam-

age score (15 points=maximum); ocular surface epithelial damage score (9 points=maximum); and the Schirmer I test.

In all FBUPs, eye dryness and fatigue were the worst symptoms. Symptoms specific to different types included: for AB, sensitivity to light, heavy eyelids, pain, foreign body sensation, difficulty opening the eye, and discharge; for SB, heavy eyelids; and for LB, foreign-body sensation. Statistically significant differences ( $p<0.05$ ) were found in: tear meniscus radius (AB vs. SB, AB vs. DB, AB vs. RB, and LB vs. RB); tear film lipid layer interference grade (AB vs. all other FBUPs, LB vs. SB, and LB vs. DB); tear film lipid layer spread grade (AB vs. all other FBUPs); fluorescein breakup time (AB vs. LB, AB vs. DB, AB vs. RB, SB vs. DB, SB vs. RB; LB vs. RB, and DB vs. RB). Significant differences were also found in noninvasive breakup time (AB vs. all other FBUPs, SB vs. DB, SB vs. RB, and LB vs. RB); corneal epithelial damage score (AB vs. all other FBUPs, LB vs. SB, LB vs. DB, and LB vs. RB); ocular surface epithelial damage score (AB vs. SB, AB vs. LB, AB vs. DB, LB vs. SB, LB vs. DB, and LB vs. RB); and Schirmer I test (AB vs. SB, AB vs. DB, and AB vs. LB).

Researchers say that the five different fluorescein breakup patterns reflect different pathophysiologies.

*Am J Ophthalmol* 2017;180:72-85.  
Yokoi N, Georgiev G, Kato H, et al.



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# New Optovue Software

**T**he U.S. Food and Drug Administration cleared Optovue's epithelial thickness mapping software for quantitative measurements of the epithelial and stromal layers of the cornea. The company says that epi-mapping is the first non-contact, quantitative method for making corneal epithelial and stromal measurements, and the only FDA-cleared product indicated to provide corneal epithelial and stromal measurements that aid in the diagnosis, documentation and management of ocular health and disease in adults.

Pre-surgical assessment with epi-

mapping can help determine whether patients are suitable for refractive procedures, and the software provides information about how the eye is healing after refractive and corneal surgery, the company says.

For more information, visit [optovue.com](http://optovue.com).

## Easyret Photocoagulator Laser

**I**n late July, Quantel Medical announced FDA approval of the Easyret 577nm yellow photocoagulator for the treatment of certain forms of macular edema and peripheral retinal pathologies.

Quantel highlights the Easyret's broad range of settings for treatment of pathologies such as diabetic retinopathy, macular edema and central serous chorioretinopathy. With the new Easyret, surgeons can select MultiSpot mode for a pattern of simultaneous targets of treatment, and it also comes equipped with SubLiminal mode, enabling surgeons to customize a train of short pulses to manage the thermal impact on targeted tissues.

For more information on Quantel Medical's Easyret, visit [quantel-medical.com/products/52-easyret](http://quantel-medical.com/products/52-easyret).

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A severe ocular chemical injury results in limbal stem cell deficiency for a young patient.

*Aditya Kanesa-Thanan, MD; Christopher J. Rapuano, MD; Kristin M. Hammersmith, MD*

## Presentation

A 25-year-old man who worked in an auto repair shop presented the same day as getting degreaser in his right eye. He initially went to an urgent care center where his eye was irrigated before being emergently referred to a general ophthalmologist where the eye was irrigated again. He was then referred to the Wills Eye Cornea Service. We do not have a record of his ocular pH on arrival at the urgent care center, but on arrival at the Cornea Service it was 7.5.

## Medical History

The patient's ocular history was notable only for trauma to the right eye from a piece of plastic which had left a partial thickness corneal laceration inferotemporally several years prior. He had not had any previous eye surgeries. He denied any past medical history or current medication use. He had no allergies to any medications and his family and social histories were noncontributory.

## Examination

Ophthalmic examination revealed uncorrected Snellen visual acuity of 20/200 in the right eye with no improvement with pinhole, and 20/25 in the left eye. His right pupil was difficult to examine but was seen to be somewhat reactive in the slit lamp. The left pupil was briskly round and reactive. No afferent pupillary defect was present. Extraocular movement and confrontational visual fields were full in both eyes. Intraocular pressures were measured by applanation at 16 mmHg in the right eye and 18 mmHg in the left eye. External and anterior segment examination revealed ptosis of the right eye with moderate upper and lower eyelid edema and erythema. Examination of the conjunctiva revealed chemosis inferiorly with 360-degree blanching of the limbal conjunctival vessels and an almost 100-percent conjunctival epithelial defect (*Figures 1-3*). The cornea was diffusely whitened with a total epithelial defect and a partial-thickness laceration inferotemporally from the previous trauma. There was a poor view to the iris through the hazy cornea but it was seen to be flat and the pupil round, and the anterior chamber was deep. There was a hazy view to the lens but no gross abnormality was seen. The anterior examination of the left eye was normal. B-scan of the right eye demonstrated a formed anterior chamber with the lens in place, clear vitreous and a flat retina.

***What is your differential diagnosis? What further workup would you pursue? Turn to p. 64 for the diagnosis.***



Figure 1. External photograph of the right eye on day one showing hazy cornea with 360-degree blanching of the limbal conjunctival vessels. Also seen is the patient's partial-thickness laceration inferiorly from previous trauma.

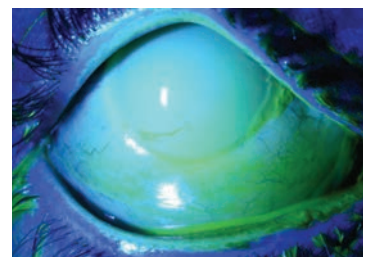


Figure 2. External photograph of the right eye on day one with fluorescein staining demonstrates a total corneal epithelial defect with large areas of conjunctival staining showing severe epithelial injury.

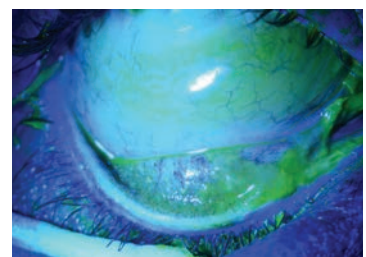


Figure 3. Eversion of the lower eyelid demonstrates palpebral conjunctival epithelial injury extending into the lower fornix.

## Diagnosis and Management

The patient was diagnosed with a Dua class VI ocular surface burn (Roper-Hall class IV) of the right eye. A ProKera sutureless amniotic membrane (Biotissue; Doral, Fla.) was placed in the right eye on day one after a discussion of the risks, benefits and alternative treatments, including suturing an amniotic membrane. The patient was started on daily Vitamin C, doxycycline 100 mg two times per day, prednisolone acetate 1% every two hours, bacitracin-polymyxin ophthalmic ointment every two hours and atropine twice per day, all in the right eye. The extremely guarded prognosis was discussed with the patient, given the severity of his injury.

The patient followed up several times in the intervening weeks and required lysis of symblepharon at the slit lamp, but over time he experienced slow conjunctival re-epithelialization and improved to counting fingers.

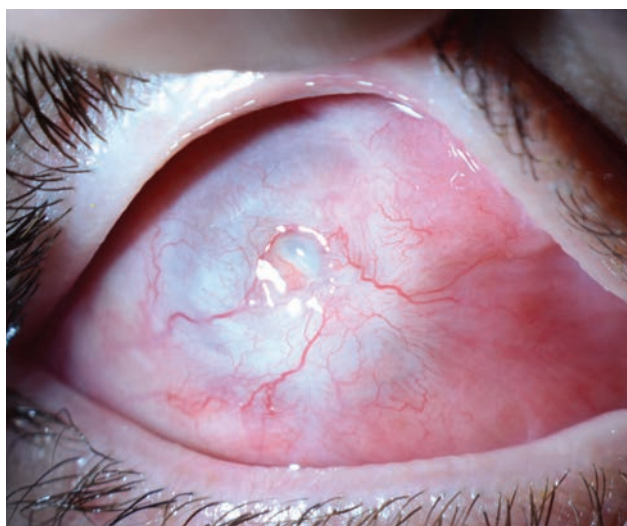


Figure 4. External photograph of the right eye at month six shows dense pannus 360 degrees and symblepharon superonasally.

The ProKera was replaced approximately one month after his injury. Around seven weeks after the initial injury the patient underwent lysis of symblepharon, double-layered sutured amniotic membrane transplant, intraoperative ProKera placement, temporary lateral tarsorrhaphy and suture of his old corneal laceration in the operating suite. About a month later he underwent further lysis of symblepharon, repeat amniotic membrane transplant and placement of ProKera. He was tapered off of his topical steroids and his epithelial defect eventually closed. He was left with dense pannus and symblepharon formation secondary to severe limbal stem cell deficiency (LSCD) in the right eye, however. Almost one year after the injury, the patient underwent superior and inferior autologous limbal stem cell transplantation with good initial results.



Figure 5. External photograph of the right eye at month six shows dense inferior pannus with symblepharon inferiorly.

## Discussion

Ocular chemical injuries are a very common occurrence and a frequent cause of urgent ophthalmic evaluation. More than 15,000 chemical eye injuries occur in the US every year, with an average age of 35 and a 2:1 ratio of males to females.<sup>1</sup> The classic teaching is that alkali injuries penetrate the ocular surface more readily through saponification of cell membranes. Acid injuries tend to coagulate surface proteins more, limiting penetration.

When faced with severe chemical injuries, the most

important treatment is immediate irrigation with a neutral pH solution. When receiving calls from patients or community emergency care centers, which are routinely the first destination for these patients, it is important to emphasize that irrigation must start immediately. The patient should be irrigated until the pH of the ocular surface is 7 to 7.5 before discharging or transferring him for further ophthalmologic care. There have been several studies demonstrating the efficacy of buffered solutions for achieving faster normalization

of pH in these cases.<sup>2</sup> However, it's important not to try to "neutralize" alkali injuries with acid solutions or acid injuries with basic solutions, as this can cause further harm.

On ophthalmologic exam, sweep the fornices to remove any particulate matter that may be embedded. The size and shape of the corneal and conjunctival epithelial defects should be measured and documented, paying special attention to the palpebral and bulbar conjunctiva. Clock hours of limbal ischemia should be noted. Phenylephrine should be avoided for dilation, as it can worsen limbal vasoconstriction.

Classification systems for chemical injuries have included the Roper-Hall classification<sup>3</sup> and the newer Dua classification.<sup>4</sup> Both systems use the epithelial defect size and the clock hours of limbal ischemia to predict visual potential in chemical injuries. The major difference between the classifications is that the Dua system subdivides the most severe chemical injuries (Roper-Hall class IV) into more categories (Dua class IV-VI) which allows for finer prognostication. For example, a Dua class IV patient with seven clock hours of limbal ischemia will likely fare better than a Dua class VI patient with 12 clock hours of limbal ischemia, but these patients would both be Roper-Hall class IV.

Treatment of ocular surface chemical injury ranges from simple for mild injuries to complex for severe ones. Sutured amniotic membrane has shown promise in moderate burns, with better visual outcomes and improved epithelialization by 21 days with nonsignificant trends towards decreased corneal neovascularization and symblepharon formation in one study.<sup>5</sup> However, there was no significant improvement in severe burns in that study, and only one of the eyes studied re-epithelialized within 21

days. Another study showed that eyes which received sutured amniotic membrane within six days after injury fared better than those that received amniotic membrane later than six days.<sup>6</sup> However, no eye with a Grade VI injury attained better than 20/400 vision, even with amniotic membrane therapy. Recent case studies have also demonstrated the effectiveness of using sutureless amniotic membrane (e.g., ProKera) early in cases of severe chemical injury to promote re-epithelialization and minimize complications.<sup>7,8</sup>

When faced with a patient with severe LCSD from an ocular surface burn, there are several options for limbal stem cell transplant.<sup>9-11</sup> In patients with unilateral injuries, conjunctival limbal autograft can be performed; this borrows several clock hours of healthy limbus from the patient's fellow eye. Cultivated limbal epithelial transplant uses less tissue but requires culture of the patient's limbal stem cells prior to implantation, which requires time and technical proficiency. Living-related conjunctival limbal allograft is an option for patients without healthy limbal tissue who have relatives willing to donate limbal tissue; keratolimbal (cadaveric) allograft is another transplant option with higher risk of rejection.

A newer procedure for patients with unilateral disease, simple limbal epithelial transplant, requires less limbal autograft tissue but doesn't require the culture of patient's stem cells prior to implantation.<sup>12,13</sup> Instead, the piece of limbus is cut into small pieces that are arranged outside the visual axis in the affected eye and secured with fibrin glue on top of an amniotic membrane. Early case reports have demonstrated good re-epithelialization of the surface with good long-term results in restoring corneal epithelium in a single surgery with minimal

donor tissue. This may prove to be a good option for patients with limited healthy limbal tissue and where donors and culture of limbal tissue are unavailable.

In summary, in this case we describe a young man with severe (Dua Class VI) alkali chemical injury resulting in severe LCSD. Even though these are challenging cases requiring prolonged follow-up with guarded expectations for recovery, there are several options for the treatment of significant LCSD that can be considered based on individual patient characteristics. **REVIEW**

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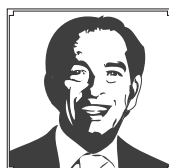
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