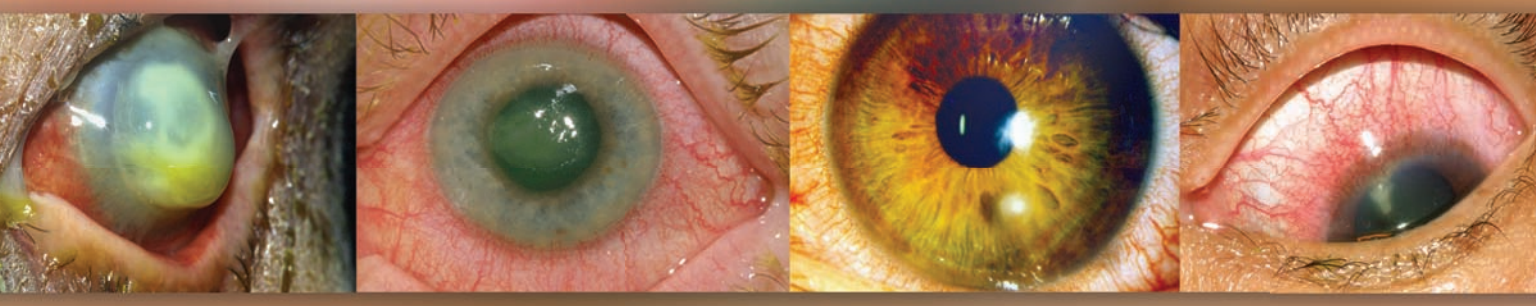
REVIEW of Ophthalmology

September 2013 • revophth.com

Cornea Issue:

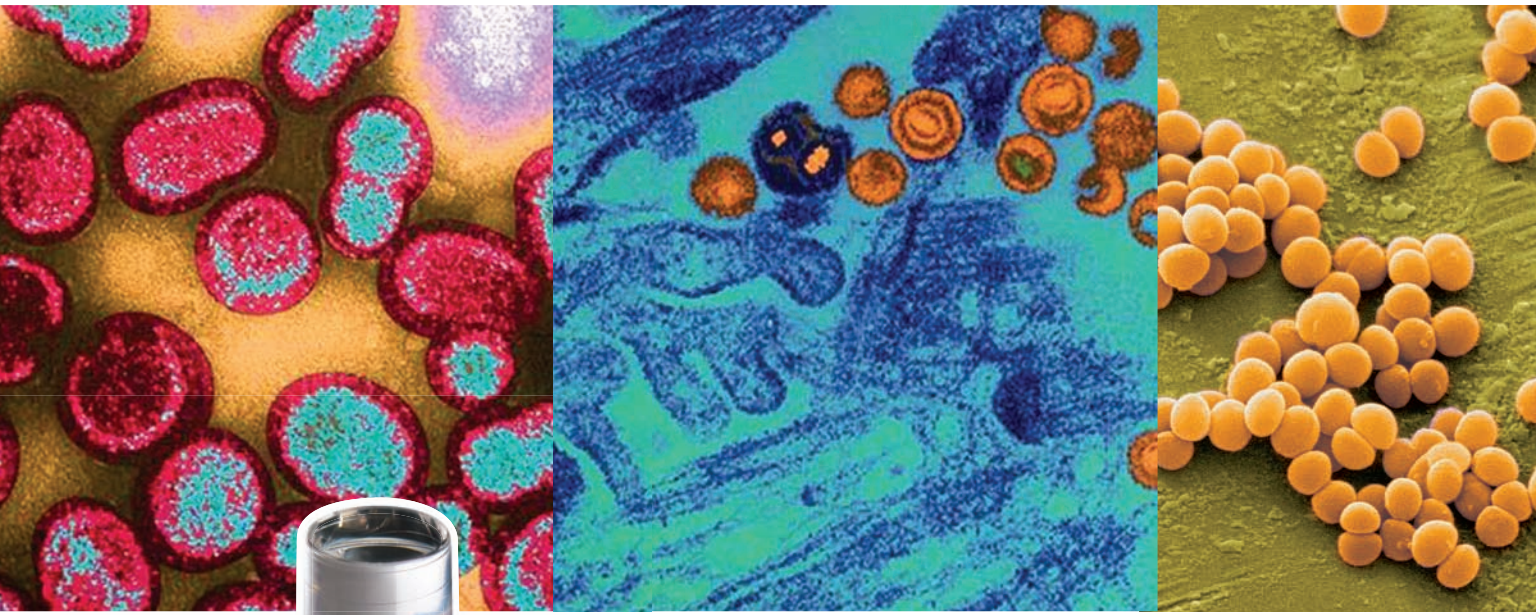
Treating Corneal Ulcers

P. 20



jmi

800.787.5426
haag-streit-usa.com



Block cross-infection without interfering with IOP.

Alcohol wipes are just not sufficient to prevent cross-infection on tonometer tips. Enter Tonosafe™ disposable prisms. According to a study in the British Journal *Eye*[1], they're just as accurate as their reusable counterparts. Your patients will thank you, too, for not passing on bacterial thugs.

Order a Free Box of 20 Tonosafes

Try Tonosafe disposable prisms for yourself. Call 800.787.5426, or visit **hs-tonosafe.com**

[1] The Scientific Journal of the Royal College of Ophthalmology

The Superior Practice.

HAAG-STREIT USA

REVIEW NEWS
Volume XVI • No. 9 • September 2013

Novel Drug-Delivery Method May Reduce AMD Injections

Johns Hopkins biomedical engineers have teamed up with clinicians to create a new drug-delivery strategy for neovascular age-related macular degeneration. In addition to testing a new drug that effectively stops neovascularization in mice, the team gave the drug a biodegradable coating to keep it in the eye longer. If proven effective in humans, the engineers say, it could mean only two or three injections per year instead of the monthly injections that are the current standard of care.

The new drug, in its time-release coating, was tested in mice with abnormalities similar to those experienced by people with wet AMD. A description of the study results, currently available online, will be published in the October issue of the journal *Biomaterials*.

"If you lose central vision, you can't drive a car and you can't see your grandchildren," says Jordan Green, PhD, assistant professor of biomedical engineering and ophthalmology at the Johns Hopkins University. "You're willing to do what it takes to keep your sight. We hope that our system will work in people, and make invasive treatments much less frequent, and therefore easier to comply with, and safer."

Approximately 200,000 Americans suffer from central vision loss caused by wet AMD and are treated with frequent (as often as once a month) injections into the eye of a drug that blocks one of the major stimulators of abnormal blood vessel growth. "The frequent visits for injections are a burden and each injection carries a small risk of infection, so one of our goals is to find new approaches that allow for fewer visits and injections." says Peter Campochiaro, MD, the George S. & Dolores Doré Eccles Professor of Ophthalmology & Neuroscience at Johns Hopkins.

Dr. Green's laboratory, which specializes in designing new drug-delivery systems, worked with Dr. Campochiaro and Aleksander Popel, PhD, professor of biomedical engineering, whose laboratory discovered the new drug—a short piece of protein that blocks the growth of unwanted blood vessels. (The drugs currently on the market for treating wet AMD are longer protein pieces or full-length proteins that could become inactive if given a biodegradable coating.)

When the team tested the drug on cells grown in the lab, they found that it killed blood vessel cells and prevented growth of new blood vessels. The same effect was found when the drug was injected into the eyes of mice with abnormal blood vessels like those seen in wet AMD, but, as with the current standard treatment, the drug was only effective for about four weeks since the watery contents inside the eye gradually flushed it out.

The team's solution, says Dr. Green, was to slow the release and depletion of the drug by covering it in non-toxic, biodegradable coatings. They first created nanoparticles filled with the drug. When the spheres were placed in a watery environment, the water gradually broke down the coating and released the drug a little at a time. To maximize this effect, the team created larger spheres, called microparticles, filled with about a hundred nanoparticles per microparticle, and held together by another type of biodegradable glue. Testing their microparticles in mice, the team found that the drug persisted in their eyes for at least 14 weeks, more than three times as long as the current treatment. Dr. Green says that the treatments may last longer in humans than in mice, but clinical trials will not begin before further testing in other animals.

Protein Spurs Angiogenesis

A team at the University College London has reported the discovery of a protein that encourages blood vessel growth, and especially the kind that characterize diseases as diverse as cancer, age-related macular degeneration and rheumatoid arthritis. The report appeared in the journal *Nature*.

The team at the UCL Institute of Ophthalmology discovered the new protein, called LRG1, by screening for mouse genes that are over-expressed in abnormal retinal blood vessels in diseased eyes.

In these diseased retinas, the LRG1 protein is expressed by blood vessel endothelial cells, which line blood

(continued on page 6)

Ophthalmic Product Development Insights

Matthew Chapin and Brian Campion, PhD • Ora Inc., Andover, Mass.

You find yourself at a juncture where you believe you have an innovative ophthalmic product on your hands, one that could be of significant value to stakeholders (patients, physicians, payors). You have sought input from experts and they agree you have something; the concept is solid, the data is supportive, the medical and market needs are clear. Now, however, you realize that to advance the concept requires large amounts of money and additional expertise. So now what? You've resolved to seek investors. What considerations are there for financing?

What's the Plan?

Before approaching investors, it's critical to have thought through your business plan. This will include the company profile and operational structure, the Target Product Profile, or TPP (see March 2013 column, "Begin with the End in Mind"). Specifically: its features and benefits beyond existing offerings; the development plan and requirements to support the TPP; the competitive landscape (both commercial and development pipeline); determining who is going to pay for your product and why (how the differential profile will support reimbursement, will patients pay out of pocket etc.); and importantly, the financial requirements. Plotting out when you can reasonably achieve value inflection points, including but not limited to preclinical and clinical proof of concept, and achieving regulatory feedback that supports the TPP will significantly affect how and when you plan to raise money.

It's important to acknowledge that your investors are looking for promising businesses, not science fairs. In considering the investor perspective, mapping out key development milestones as value inflection points will allow you to model realistic financing scenarios and focus on activities that provide step-ups in value. This will provide a road map that supports successive rounds of fundraising, ensuring you have enough runway capital to support the company during fundraising windows while being as lean and capital-efficient as possible. Development milestones that support significant step-ups in value will provide prospective investors the incentive to invest in your program based on the potential return at each value inflection point. Generally speaking, in their financial models, venture capitalists typically target an approximate 100 percent internal rate of return, which translates to three to four times over a couple of years, and approximately 10 times over four years. Now let's profile what the different investors can do to advance your product concept.

Funding: Family, Friends, Angels & VCs

Since 2008, venture capital investment is increasingly difficult to secure due to the contraction in both the number of Life Science VC firms and the total capital allocated to them by their limited partners. Generally, VCs have shifted away from investing in early-stage programs due to the high risk associated with them, coupled with a lack of historical returns.

Most life science exits are realized via company purchase (merger & acquisition) or a licensing/option deal before your product generates a single dollar of sales. Alternatively, investors may exit via the company accessing the public markets, but only recently has the initial public offering window opened. As an ophthalmic innovator, your goal is to advance your program towards commercialization while optimizing the potential return on investment for founders, employees and investors. It's necessary to have a well thought-out development plan with clear milestones in place to maximize ROI and appropriately frame an investment for investors. It will guide you towards securing follow-on financing rounds via realistic company valuations achieved at predefined value inflection points (such as achieving first human proof-of-concept).

The estimated 756,000 Angel Investors, wealthy individuals who maintain a net-worth over $1 million, are a good place to start your fundraising campaign. Angel investors typically provide seed capital for projects to reach an initial inflection point. Angel groups may co-invest with institutional investors, making them an ideal target for early-stage life science financing. Not surprisingly, the last quarter of 2012 and first quarter of 2013 saw a spike in angel dollars allocated to health-care deals compared to the first quarter of 2012. Active syndicates of angel investors include Sand Hill Angels, Golden Seeds, New York Angels and Tech Coast Angels.

Occasionally, validated product concepts can avoid the family and friends (F&F) round and receive a series A or angel round. That said, it is common to turn to friends and family for the initial capital required to advance your product concept towards an investment from a VC or an angel group. Typically, F&F financing rounds occur in the seed stage before professional investors are willing to invest. The advantage of starting with F&F is that these investors are typically low-information investors who will not drive aggressive term sheets. While F&F rounds will typically have more company-favorable terms vs. institutional investment, these rounds consist of dozens of individual investors in order to raise enough money to move the project to a value inflection point. The downside of F&F is that this group is likely to get significantly diluted in future rounds of fundraising, as they may not have the resources to participate. Managing expectations with these large groups can be time intensive and challenges can arise where one has to balance follow-on round valuation and dilution issues.

Strategic Investors/Partnerships

Corporate Venture Capital has grown dramatically in the last decade to fill the void as traditional venture has contracted and moved away from early stage, higher-risk investments. Importantly, these firms help provide big pharma and device companies the opportunity to avoid an innovation gap and thus provide products needed to supplement product development pipelines. This has also been valuable to offset pharma's business-development groups who have moved towards licensing and acquiring later-stage development programs that are significantly de-risked via costly clinical efficacy studies. Many early stage Series A and Series B rounds of financing

have CVC in the investor syndicate. Pharma understands corporate venture activity is essential to the health of the early-stage ecosystem that the industry relies on for future product innovation.

Pharmaceutical companies are not the only strategic investors. Clinical service organization (CROs), and Payors & Providers may also provide investment into your development program. CROs represent an increasingly valuable source of capital for product innovators. A recent case study includes a small start-up company developing a new product for an ophthalmic indication. The company approached and selected Ora Inc. to work with them and partner on the regulatory filings, Phase II trial, business strategy, and support for positioning to potential pharma partners. Following Phase II, the road show resulted in a non-dilutive upfront payment from a pharma partner in exchange for an exclusive global option to that pharma for the product. The up-front option, non-dilutive payment supports the costs of the later-stage clinical trial. This example shows how a VC-backed, small start-up, a strategic CRO partner that is expert in the space, and pharmaceutical exit partner can work together to take a product through Phase II, and then support development through Phase III.

Transferring an equity stake or milestone and royalty payments in exchange for a reduced cost for preclinical development, clinical trial and consulting services will advance product concepts that would be unable to proceed due to the rate-limiting cost of clinical trials. A reduced clinical trial cost will decrease founder dilution and make your life as an ophthalmic innovator easier due to the reduced amount of capital required to reach value inflection points and subsequent step-ups in your program's valuation.

Non-Traditional Sources

Foundations provide grants that represent non-dilutive seed capital to conduct initial research and advance product concepts towards human clinical studies. While some foundations will fund clinical trials, grants are typically designed to cover costs for translational research and investigational new drug-enabling studies.

Ophthalmic-specific foundations such as Foundation Fighting Blindness, the National Neurovision Research Institute and the Glaucoma Research Foundation look to fund novel research to treat ophthalmic diseases

(continued on page 77)

(continued from page 3)

vessel walls. LRG1 is also present in the eyes of patients with proliferative diabetic retinopathy.

The study shows that, in mouse models, LRG1 promotes angiogenesis. Conversely, inhibition of LRG1 in mouse models reduces the harmful blood vessel growth associated with retinal disease.

The authors of the study suggest that blocking LRG1's activity is a promising target for future therapy.

Professor John Greenwood, senior author of the research from the UCL Institute of Ophthalmology said: "We have discovered that a secreted protein, LRG1, promotes new blood vessel growth and its inhibition prevents pathological blood vessel growth in ocular disease.

"Our findings suggest that LRG1 has less of a role in normal blood vessel growth and so may be particularly applicable to 'bad' blood vessel growth. This makes LRG1 an especially attractive target for therapeutic intervention in conditions where vessel growth contributes to disease."

Angiogenesis plays a role in many diseases where new vessel growth can be harmful: in the retina, uncontrolled and irregular blood vessel growth in diseases such as AMD and diabetic retinopathy; and in the growth of cancerous solid tumors. Angiogenesis is also an important feature of rheumatoid arthritis, where it contributes to the inflammation of the joint.

The mechanism by which LRG1 promotes angiogenesis is by modifying the signaling of a multifunctional secreted growth factor called transforming growth factor beta. TGF-beta regulates both the maintenance of normal blood vessels, and the unwanted growth of harmful blood vessels, but precisely how it promotes two opposing outcomes is a biological paradox.

This study indicates that in the retinal diseases investigated, LRG1 production is "turned on" in blood vessels. This causes a switch in TGF-beta signaling away from a normal vessel maintenance pathway towards a pathway that promotes the growth of new, harmful blood vessels.

Professor Stephen Moss, senior author from the UCL Institute of Ophthalmology said: "Genetic studies have revealed that the gene that codes for LRG1 is conserved in vertebrates, and this study confirms that mouse and human blood vessels express LRG1.

"We predict, therefore, that abnormal blood vessel growth is also a conserved process and that the role of LRG1 is equally applicable to human pathological angiogenesis."

He added: "Work is already under way to develop a therapeutic antibody that targets LRG1."

Study Shows Role for Complement

Researchers at the Massachusetts Eye and Ear Infirmary, Harvard Medical School, report the unexpected finding that in mice genetically engineered to have an inherited form of macular degeneration, turning off the animals' complement system, a part of the immune system, prevented the disease. Their work was published in mid-August in *Human Molecular Genetics*.

This is the first report to demonstrate a role for the complement system in an inherited macular degeneration. Previous genetic studies have shown that variants in the genes that encode several complement system components are important risk factors for AMD. Based on this, drugs that inhibit specific complement system activities are being tested clinically as treatments for AMD. However, it is not entirely clear how alterations in complement system components lead to AMD.

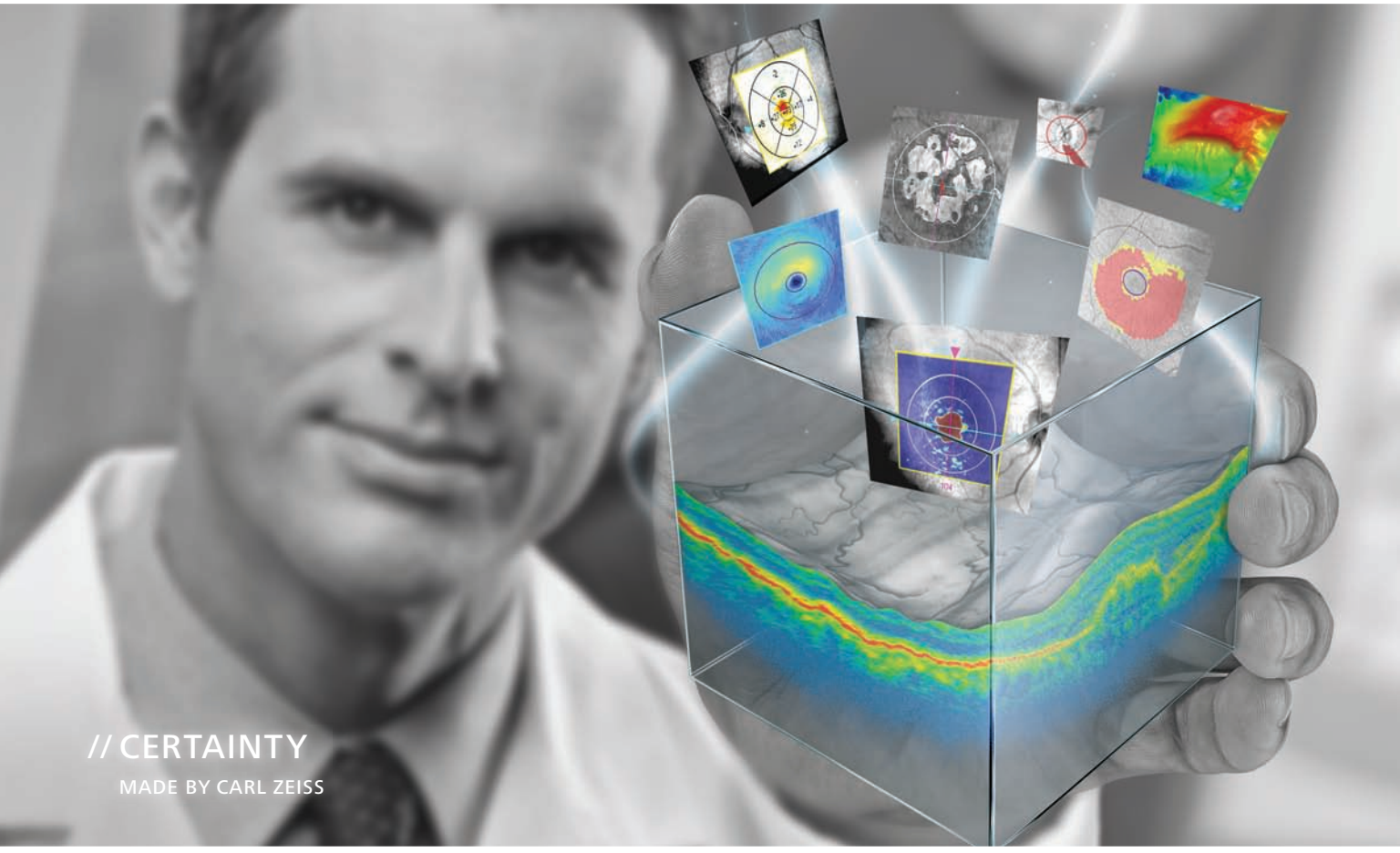
The results reported suggest that complement activation by abnormalities in the extracellular matrix or the scaffold secreted by retinal cells plays an important role in the formation of basal deposits, one of the earliest stages of macular degeneration. Basal deposits are precursors of drusen; their presence is the first clinical indication of a risk of developing macular degeneration.

The findings are important because they suggest that inherited macular degenerations share common features with AMD, such as a complement-mediated response to abnormal extracellular matrix. The results also suggest that alterations in the activity of the complement system are involved in the earliest stages of disease pathogenesis. This finding has important implications for the use of drugs that modulate the complement system for treating macular degenerations.

For these studies, the investigators used a mouse model of inherited macular dystrophy. As a first step in their studies, the researchers used proteomic techniques to identify the proteins present in the basal deposits of the mice. Like they do in people, these deposits form between the retinal pigment epithelial cells and Bruch's membrane, composed of extracellular matrix. These studies showed that the basal deposits are composed of normal extracellular matrix components that are present in abnormal amounts. This is logical because the EFEMP1 protein is secreted by retinal cells and is thought to be required for maturation of elastin fibers, which are part of Bruch's membrane.

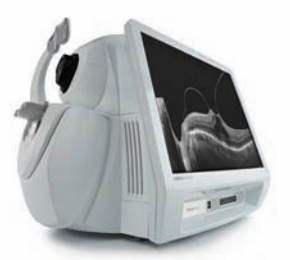
The proteomic analyses also suggest that the altered extracellular matrix stimulates a local immune response, including activation of the complement system. The complement system is part of our innate immune system, and helps fend off infections, but under certain circumstances can also lead to cell and tissue damage. REVIEW

It's not what makes each member
of the CIRRUS family unique,
it's what makes them the same.



CIRRUS SmartCube

Puts answers within reach



SmartCube™ is the core of the CIRRUS™ family. It helps you turn micro-structural information into new strategies in care. With extensive applications for smarter analysis and faster throughput, the power of the CIRRUS SmartCube means better decision-making is at hand.

CIRRUS. The Smart OCT.

ZEISS

We make it visible.

Carl Zeiss Meditec, Inc. 800 342 9821 www.meditec.zeiss.com/cirrus

REVIEW Editorial Board

Contributors

Advisory Board

Jobson Professional Publications Group

BUSINESS OFFICES
11 CAMPUS BOULEVARD, SUITE 100
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
SALES MANAGER, NORTHEAST,
MID ATLANTIC, OHIO
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

SALES MANAGER, SOUTHEAST, WEST
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

VICE PRESIDENT OF OPERATIONS
CASEY FOSTER
(610) 492-1007 CFOSTER@JOBSON.COM

MANAGER EDUCATIONAL CONFERENCES/MEETINGS
MEG McDONALD
(610) 492-1045 MMCDONALD@JOBSON.COM

PRODUCTION MANAGER
SCOTT TOBIN
(610) 492-1011 STOBIN@JOBSON.COM

SUBSCRIPTIONS
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL: **RHSUBS@HALLDATA.COM**
CIRCULATION E-MAIL: **RHSUBS@HALLDATA.COM**

CIRCULATION
PO BOX 2026, SKOKIE, IL 60076
(877) 529-1746
OUTSIDE USA: (847)763-9630
FAX: (847)763-9631

SENIOR CIRCULATION MANAGER
ANTHONY GUADAGNINO
(212) 219-7870 aguadagnino@jobson.com

CHIEF OPERATING OFFICER
JEFF MACDONALD

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, HUMAN RESOURCES
LORRAINE ORLANDO

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

VICE PRESIDENT, CIRCULATION
EMELDA BAREA

jmi

100 Avenue of the Americas
New York, NY 10013

REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information. 100 Avenue of the Americas, New York, NY 10013-1678. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 2026, Skokie, IL 60076, USA. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (847) 763-9631. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.V

Trade Up To Keeler

Trade-in your old Kowa hand-held slit lamp & get $600 towards Keeler's Advanced PSL Classic!

Powerful & Portable!

- Precision machined aluminum chassis
- Advanced optics, x10 & x16 magnification
- Controllable illumination from maximum to zero
- Most Apertures and filters along with 1.mm square light patch for assessing a/c flare

Trade-in & Special Bonus
FREE iPhone 4 Adapter and Carrying Case.
Offer expires December 31, 2013.

Buy Online!
keelerusa.com

Keeler
OPTICS

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

LET'S TALK SOLUTIONS

Accutome's AccuSharp™ Guarded Ophthalmic Knives offer superior sharpness and safety at an affordable price. It provides sharps protection for you, your staff and your budget!

Call today or use the QR Code to trial the AccuSharp Guarded Knives.

www.accutome.com/accusharp-guarded-trial-request

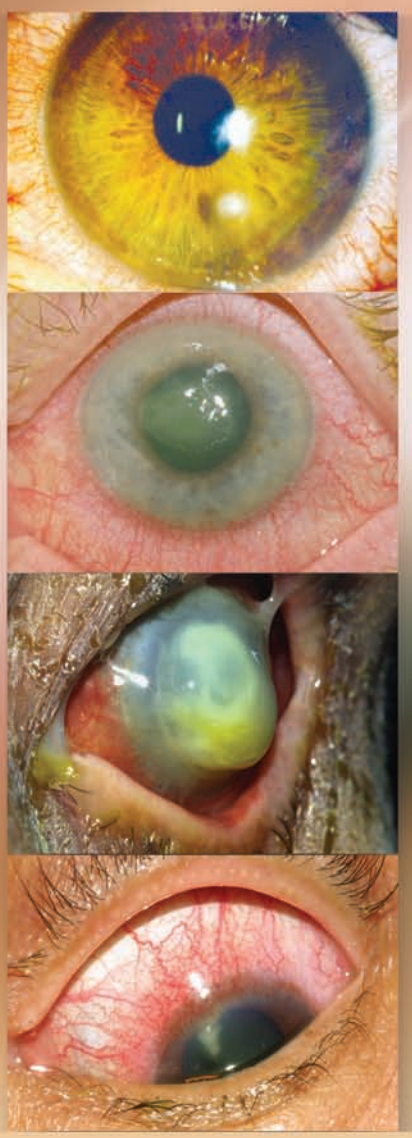
ACCUTOME®
A HALMA COMPANY

3222 Phoenixville Pike, Malvern, PA 19355 USA • 800-979-2020 • 610-889-0200 • FAX 610-889-3233 • www.accutome.com

REVIEW® of Ophthalmology

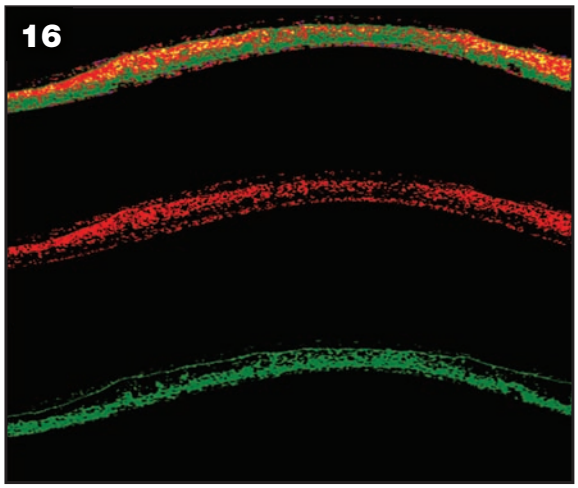
September 2013 • Volume XX No. 9 | revophth.com

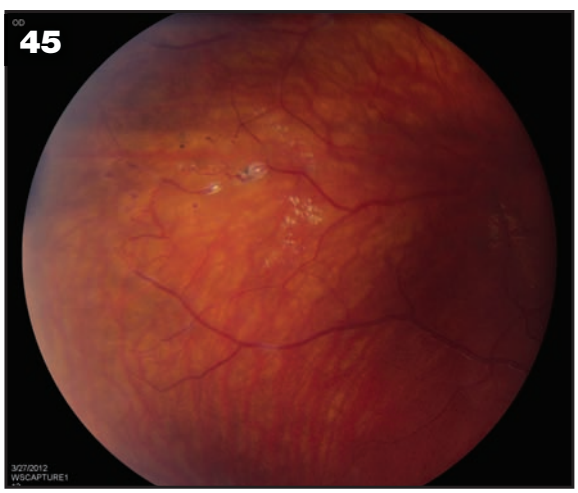
Cover Focus

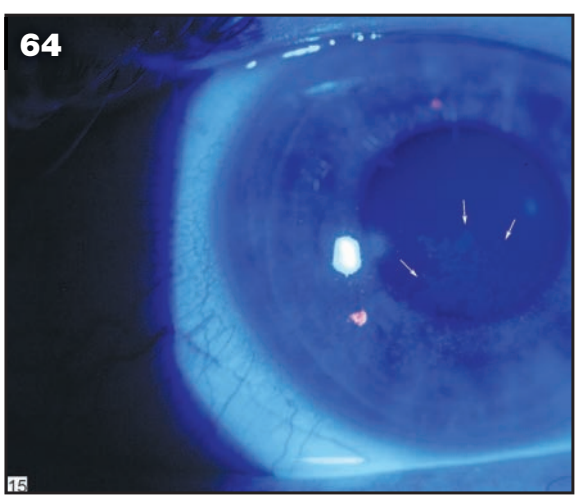


Cover images:
John Sheppard, MD, MMSc

Departments







TREAT EARLY...

A SIMPLE CORNEAL SCAR IS ALL IT TAKES TO CHANGE AN OUTCOME

Treat early with PROKERA® SLIM, biologic corneal bandage, to reduce inflammation, promote healing and minimize the risk of scarring.

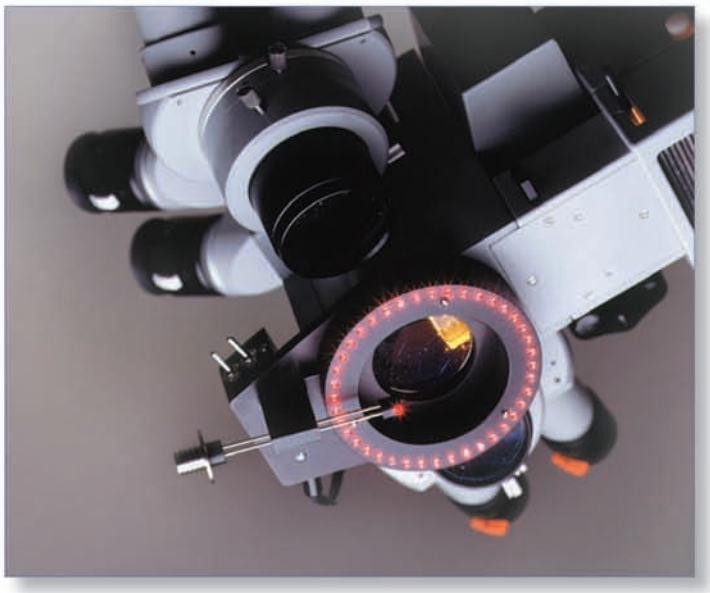
biotissue™

www.biotissue.com
8305 NW 27th Street, STE 101
Miami, FL 33173 – 888-296-8858

NEW PROKERA® | Slim

The sooner the better.

Call 888-296-8858 | or visit www.prokerainfo.com



360° FIXATION TARGET / OPERATIVE KERATOMETER

The simple inexpensive add-on to the operative microscope gives the surgeon instant qualitative operative keratometry at any time. It eliminates worry about ocular torsion when the patient lies down as it identifies positively the appropriate axis for astigmatic keratotomy. It eliminates the chilling possibility of a "90 degree error". Its movable fixation light can be rotated continuously over 360° to have the patient fixate on whatever position is best for the surgeon to make incisions. It is the ideal instrument to facilitate astigmatic keratotomy with cataract and refractive lens surgery.

CHAN WRISTREST

The Varitronics Chan Wristrest is the standard for stabilization of the surgeon's hands for ophthalmic surgery. Its height is easily adjustable and its bar can be rotated to adjust the distance to the patient's eye. It allows for the stabilization of the surgeon's arm and wrist to permit maximum control of the fine finger movements necessary for eye surgery. Its long aluminum base plate which is placed under the operating table pad makes it adaptable to any operating table. Like all Varitronics equipment, it is built to last indefinitely.

SURGICAL STOOL

The Varitronics hydraulic surgical stool is the ideal stool for the eye surgeon. It has a large comfortable seat, wide stable base, and foot bar/height control which allows the surgeon to change the height of the stool easily and gently by foot while operating.

NEVYAS DRAPE RETRACTOR

Increase patient comfort by keeping the drape away from the patient's nose and mouth. Reduce patient anxiety.

AUTOSWITCH CONTROL SYSTEMS

Varitronics Ophthalmic Control Systems will control your room and fixation lighting automatically and put your instruments at your fingertips. In-cabinet and desktop models available.

ETL Approved

EYEDENTIFIERS

Be certain which eye is to be operated.

VARITRONICS

See us at AAO Booth #3729

CALL TOLL FREE

800-345-1244

ph: 610.356.3995 / fax: 610.356.5222
e-mail: varimed@varitronics.com
www.varitronics.com

REVIEW® of Ophthalmology

New Ideas Must Still Meet Old Standards

Nearly every week, you can find an interesting "future of medical practice" story. It seems a given that two of the key changes in the way medicine is practiced will involve remote wireless monitoring and greater use of e-communications. A couple of recent studies show that the success of these new notions still depends on some old concepts: They have to be simple for the patient, and they have to be worth the doctor's time.

Joseph Kvedar, MD, the director of the Center for Connected Health at Partners Healthcare (connectedhealth.org) recently described a study he published that looked at two home-hub transmission technologies. Patients with diabetes were asked to check their glucose twice a day and upload the results to a database (via the Internet). Some had a device that required them to push a button to accomplish the upload and some had a "passive sensing" wireless device that required no button push.[1] The frequency of measurements and data uploads was significantly higher in the wireless group versus the push-button group.

Using smart phones as a data upload/home hub device offers "transformational opportunities," Dr. Kvedar writes. "We can use them as a device to engage the consumer around health content. We can use them to display health-related information at just the right moment in just the right context. ... We can use them to message you in the moment with contextually relevant, motivating messages."

Messaging was the topic of the second study, specifically a formal look at the advantages and barriers to e-communications.[2]

A group at Weill Cornell Medical College in New York City studied 21 primary-care practices that regularly use e-communications with patients for such things as sending test results, receiving requests for medication refills, scheduling appointments and querying physicians. Not surprisingly, the researchers identified three advantages to e-communications: convenience for patients; patient satisfaction; and safe, high-quality care.

However they also identified a substantial disadvantage: the additional work for providers. The volume of electronic messages ranged from a low of five to 10 messages per provider per day to a high of 20 to 50. For some physicians, the work produced "the feeling of never being done," the authors report.

But the biggest barrier was the still-evolving issue of reimbursement for time spent in such activity. "Despite the fact that we found experiences with electronic communications were, on the whole, very positive in the groups we studied that have embraced this technology, we believe the big stumbling block to its widespread use around the country will be compensation," the lead author said. "Until different payment models emerge, electronic communication is unlikely to be widely adopted by physician practices."

1. J Diabetes Sci Technol 2013 May 1;7(3):623-9
2. Health Aff August 2013;32:1361-1367.


Enhancing OCT: New Ways to See More

Advances in technology are allowing the visualization of ever-greater detail—with potentially important clinical consequences.

Christopher Kent, Senior Editor

Once a technology such as optical coherence tomography becomes available, there's inevitably an effort to improve its accuracy and allow it to detect ever-more-detailed information. Two recent developments are helping to do exactly that.

Quantifying Reflectivity

A new software system referred to as CORDA, developed at Diopsys, a medical instrumentation company in Pine Brook, N.J., performs a unique analysis of basic B-scan information output by any of the existing SD-OCT machines. It aims to provide a means to specify the type of changes taking place inside the retinal nerve fiber layer and potentially detect signs of glaucomatous damage earlier than current OCT algorithms.

Neuroophthalmologist Alberto Gonzalez, MD, is the inventor of the CORDA software. "We noted that different optic nerve edemas produce different reflectivity in OCT images," he explains. "For example, if edema of the optic nerve is caused by an infectious disease, it tends to be more reflective than if it's caused by an immunologic disease such as multiple sclerosis. That convinced me that it might be valuable to quantify the reflectivity of the OCT image."

Dr. Gonzalez points out that different reflectivity in OCT images correlates with different components of the retinal nerve fiber layer. "The current OCT algorithms use reflectivity to find the boundaries of the different layers of the retina," he says. "However, the structures inside the retinal nerve fiber layer each have a different index of reflectivity. Those differences can also be detected in the resulting OCT image.

"CORDA stands for Color Reflectivity Discretization Analysis," he adds. "Discretization is a known math calculation that allows us to group together sections of a continuous scale—the color scale in this instance—so we can quantify them for the purpose of analysis. Without this kind of grouping, quantifying the colors detected by the OCT machine would be impossible."

Working with this technology in glaucoma patients, the team noted that the retinal nerve fiber layer changes in reflectivity as glaucoma progresses. "During the glaucomatous process, ganglion cells die because of apoptosis," he explains. "Unlike necrosis, apoptosis is characterized by a disappearance of structure, causing the reflectivity to decrease over time. By monitoring this, CORDA allows us to detect glaucomatous change and how fast it may occur.

"Current SD-OCT measurements of the thickness of the retinal nerve fiber layer are confounded by the presence of multiple tissues inside the layer," he continues. "For example, it's well known that there's great variability in retinal blood vessels between individuals. Other structures such as glial cells and supportive tissues can also cause errors in your reading. Even vitreoretinal traction can alter retinal nerve fiber layer thickness. But CORDA can isolate what really represents axons inside the RNFL, thus telling you their condition without including the confounding factors."

Supporting Data

Dr. Gonzalez says his group is currently preparing two papers regarding CORDA for publication. "One paper presents data regarding the repro-

The potential in the refractive market is growing.

How do you cultivate the opportunity for your practice?

When you provide patients with the opportunity to use financing options with the CareCredit® healthcare credit card, they can fit the refractive procedures they want into their monthly budget. Now, the potential for growth is expansive. Nearly 80 million members of Generation Y are moving into the ideal age for LASIK procedures*, while millions of Baby Boomers are becoming candidates for premium IOLs, lifestyle lenses, and more. CareCredit can help you plant the seeds to cultivate your share:

- A Practice Development Team dedicated to your success.
- A network of 7+ million cardholders approved for financing.
- A suite of FREE resources to maximize your practice's potential.

Millions of refractive opportunities are waiting.
Let's start cultivating your share now.

CareCredit℠
Making care possible...today.

CareCredit.com • 800.859.9975 option 1, then 6

*United States Census Bureau, *"2010 Census Briefs – Age and Sex Composition: 2010, Table 2"* (2011).

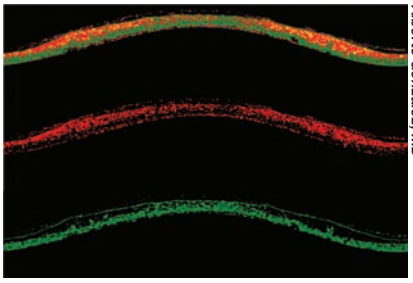
ducibility of CORDA's analysis," he says. "The second paper presents data showing that CORDA is able to detect damage in the structure of the RNFL more accurately than the current OCT algorithms.

"One of the studies we discuss in the second paper relates to CORDA's ability to detect structural damage in glaucoma suspects," he continues. "The standard algorithms and CORDA are both good at differentiating between healthy eyes and glaucomatous eyes, but CORDA does a much better job of detecting abnormalities in glaucoma suspects. This could have important clinical ramifications.

"Another finding with important implications has to do with the current idea that damage mostly occurs in the inferior and superior sectors of the RNFL, primarily affecting the magnocellular system," he adds. "CORDA also found abnormalities in the temporal and nasal sectors. That supports the novel idea that the parvocellular system is also affected, and that furthermore, it may be affected before the magnocellular system."

L. Jay Katz, MD, director of the Glaucoma Service at Wills Eye Hospital, and coworkers have collaborated with Dr. Gonzalez to examine the potential role of CORDA in glaucoma evaluation. "CORDA seemed to segregate retinal ganglion cells from glial support tissue, with a correlation between retinal ganglion cell thickness and functional testing on perimetry," says Dr. Katz. "The potential ability to differentiate retinal ganglion cells and support glial tissue may be a huge step forward in early detection of glaucoma and disease progression. My enthusiasm for CORDA is high, based on the information generated thus far."

Dr. Gonzalez says the company hopes the CORDA software will be available soon; at this writing it is under consideration by the Food and Drug Administration.



Alberto Gonzalez, MD

A discretization of a retinal nerve fiber layer OCT image using the CORDA system. Red and yellow represent axons; green represents glial and other supportive tissue.

Enhanced Vitreal Imaging

Another new approach, utilizing a prototype swept-source OCT system, is enabling enhanced 3-D imaging of the vitreous, revealing many potentially clinically useful details that were not visible previously. Two individuals working with the new approach, Jonathan Liu, a PhD candidate in Professor James Fujimoto's group at the Massachusetts Institute of Technology, and Andre Witkin, MD, a vitreoretinal surgeon at the New England Eye Center and assistant professor of ophthalmology at Tufts University School of Medicine, explain.

"Our prototype system images at 100,000 A-scans per second and uses long wavelengths," says Mr. Liu. "While spectral domain OCT detects signals using a spectrometer and camera, swept-source OCT uses photodetectors with a swept laser, which are significantly more sensitive. With SD-OCT the sensitivity decreases across the imaging range; swept-source OCT maintains high sensitivity over a long range, producing a good signal in the vitreous, all the way to the choroid."

Mr. Liu explains that their team combined this capability with two other innovations to allow unprecedented scanning of the vitreous. "An OCT signal has approximately 40 dB of dynamic range," he says. "A computer monitor can only display about 256 gray levels, so OCT images are typically displayed with a logarithmic intensity scale in order to show their full dynamic range. However, this makes it hard to see subtle changes in regions of weaker signals, such as the vitreous. So we took the signals coming from the vitreous and displayed them using a scale that makes its features much more visible. We also applied motion-correction algorithms which enabled averaging multiple 3-D data sets. This, combined with the higher imaging speed of swept-source OCT, allows much clearer 3-D imaging of the vitreous.

"As we reported at this year's ARVO meeting, this technology allows us to see the bursa premacularis, or posterior precortical vitreous pocket; the area of Martegiani, or Cloquet's canal; the Bergmeister papilla; and posterior hyaloid detachment," he continues. "We saw multiple granular opacities in different spaces in the vitreous, including the vitreous cortex, Cloquet's canal and the posterior precortical vitreous pocket."

Dr. Witkin notes that the development of new drugs that act at the vitreomacular interface, such as ocriplasmin, has renewed interest in the visualization of vitreomacular interface abnormalities. He adds that it's possible to obtain cross-sectional images of the vitreous with SD-OCT technology by displaying orthoplanes from the 3-D volumes and adjusting the dynamic range and contrast of the images. "However, swept-source OCT has advantages, such as increased imaging speed and no signal drop-off over the imaging range, that make it the best for imaging the vitreous in 3-D, especially when combined with the other software enhancements mentioned previously," he says. "One of our hopes is that if visualizing microscopic changes in the vitreous has significant clinical utility, manufacturers will be encouraged to make swept-source OCT a part of their commercial OCT product lines." REVIEW

Everybody Knows Children Deserve Special Treatment!

NEW From the Maker of the #1 Doctor Recommended Eyelid Cleanser

OCuSOFT® Baby™ Eyelid & Eyelash Cleanser is a clinically trusted, tear-less formula that gently removes morning gunk and irritants that may contribute to discomfort associated blocked tear ducts, pink eye, allergies and other eyelid related conditions. Contains no parabens, fragrances, dyes or Quaternium-15 and is ideal for children of all ages.

For FREE samples, call (800) 233-5469 or visit

www.ocusoftsamples.com

OCuSOFT®

Trusted Since 1986

www.ocusoft.com

Winning the Battle Against Corneal Ulcers

Christopher Kent, Senior Editor

Four experts share their knowledge and experience dealing with these sight-threatening lesions.

Corneal ulcers are a common problem, often encountered by eye-care professionals. Unfortunately, an ulcer can be difficult to diagnose; its cause can be elusive; and the consequences of an error in diagnosis or treatment can be severe. Knowing what to look for and common mistakes to avoid can make all the difference.

Common Encounters

"The most common type of ulcer clinicians are likely to see, by far, is a bacterial ulcer," says John Sheppard, MD, MMSc, president of Virginia Eye Consultants, professor of ophthalmology, microbiology and molecular biology, director of residency research training and clinical director of the Thomas R. Lee Center for Ocular Pharmacology at Eastern Virginia Medical School in Norfolk, Va. "Many of the organisms that cause bacterial ulcers have extremely potent tissue-destructive mechanisms, so it's always imperative that bacterial keratitis is identified and treated rapidly. *Pseudomonas*, in particular, creates proteolytic enzymes like collagenase that rapidly degrade tissues; it's known for creating ulcers that lead to perforations.

"The number one risk factor for corneal ulcers in the United States is contact lens use," he continues. "Another key risk factor is trauma. Corneal ulcers are more common among those in industrial or outdoor occupations, and being older increases your risk—particularly in the case of a very old patient who has chronic blepharitis. Diabetics are at greater risk, as are patients suffering from dry eye. Latitude is important; the warmer the climate the more likely you are to develop an ulcer, and the more likely you are to develop a fungal ulcer. In Virginia we see more fungus than in Boston; in Florida they see more than we do."

"Another ulcer that clinicians often run into is the peripheral corneal ulcer," says John R. Wittpenn, Jr., MD, partner at Ophthalmic Consultants of Long Island and associate clinical professor of ophthalmology at the State University of New York at Stony Brook. "This isn't so much an ulcer as it is a type of keratitis, an inflammatory problem associated with *staphylococcus* overgrowth in the lid. These individuals present with the classic peripheral infiltrate.

"If there's a defect, I recommend treating it as an infectious ulcer until proven otherwise," he continues. "But if the epithelium is fully intact and there's no reaction in the anterior

This article has no commercial sponsorship.

AMETEK®
ULTRA PRECISION TECHNOLOGIES

Intuitive, Inspired Pachymetry.

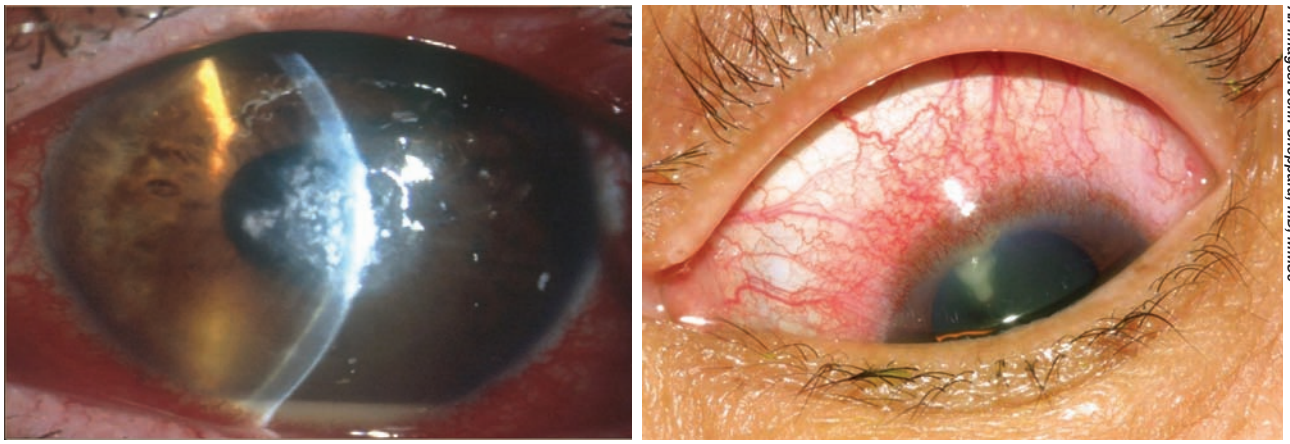
The Reichert® **iPac® Pachymeter** is the most advanced handheld pachymeter available. It features Bluetooth® wireless connectivity, one-button navigation, a rotating color LCD screen and a rechargeable lithium ion battery. Backed by an industry leading three-year warranty.

Call 1.888.849.8955, or visit **www.reichert.com/ipac**

Reichert® *is* pachymetry.

Reichert®
TECHNOLOGIES
Advancing Eye Care. Preserving Sight.™

@ReichertTech



All images: John Sheppard, MD, MMSc

The location of a corneal ulcer is an important factor in diagnosis and treatment. Above left: A central corneal ulcer with hypopyon. Above right: An aggressive chronic limbal bacterial ulcer (methicillin-resistant *staphylococcus epidermidis*) with limbal hypervascularity.

chamber, that's phlyctenular keratitis, an inflammatory problem. You should address the lids with something like AzaSite, which has great penetration, or a topical ointment applied to the lid margins at bedtime in conjunction with an anti-inflammatory. I happen to like loteprednol because it's a very good surface anti-inflammatory with a very low risk of pressure elevation. But you could also use a fluorometholone or something similar."

Of course, the difficulty of treatment and likelihood of a positive outcome are profoundly affected by how quickly the corneal ulcer is detected and treated. "When a patient comes in early, even with a virulent organism, if the infection is limited to the anteriormost part of the cornea and the patient is treated intensively with appropriate topical antibiotics, he might end up with complete resolution of the infection and just a small anterior corneal scar," notes Thomas John, MD, clinical associate professor at Loyola University at Chicago. "However, if the patient has a compromised cornea and presents later with a large corneal ulcer, even in the best scenario that can potentially result in a large corneal scar."

Dr. Sheppard points out that this issue can be exacerbated by contact lenses. "A contact lens may actually mitigate the initial symptoms of an ulcer," he says. "As a result, the patient may leave the contact lens on to make it feel better, thereby delaying presentation to the ophthalmologist or optometrist."

Identifying the Organism

Charles Stephen Foster, MD, FACS, FACR, clinical professor of ophthalmology at Harvard Medical School, and founder and president of the Massachusetts Eye Research and Surgery Institution in Cambridge, points out that when a patient presents with a corneal ulcer, a number of questions should be asked to determine the diagnosis and a reasonable first-line treatment.

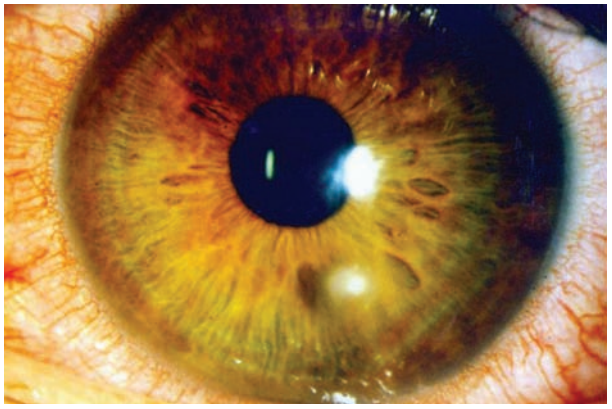
"I don't strongly promote the idea of trying to make a categorical diagnosis on the basis of clinical features, but there are a few clues that can help," he says. "Is the ulcer peripheral, near the limbus, or is it more central or paracentral? Is it just an infiltrate or a true ulcer? If it's infectious, is it bacterial, viral, fungal or parasitic? Is the patient's corneal sensibility intact or diminished? Does the patient have normal lid function? If not, is this an exposure problem? Is the patient lying asleep at night with the lids open, the cornea drying out and the epithelium breaking down? Is it a neurotrophic problem caused by nerve damage? Testing both corneas for sensation of touch can be very enlightening in that regard.

"In cases of microbial keratitis and stromal ulceration, in addition to culturing the organism, there are certain clinical cues and clues that can be helpful," he continues. "These include obvious factors such as a discharge. If there is a discharge, what are its characteristics? Is it watery or more like pus? What color is it? If the discharge resembles pus, does it have an odor? *Pseudomonas*, for example, often has a characteristic sweet smell.

"With fungus there's an infiltrate, and two or three other little white spots not connected to the infiltrate," he notes. "You may see a bit of a plaque on the endothelium, on the inside behind the white infiltrate. It's not always the case that a fungus is present when those signs exist, but the index of suspicion would be heightened if one saw those features."

Dr. Foster adds that a herpetic ulcer is another, albeit less-common possibility. "If the patient has had herpes in the past, even if he comes in with something that doesn't look like a classic dendritic epithelial defect, he may nonetheless have herpetic disease rather than a bacterial disease,"

he says. "Simply testing corneal sensation at that point can often tell you a lot. If you find tremendously depressed sensation, that might indicate a neurotrophic ulcer. If it is a neurotrophic ulcer, pursuing the wrong course—hammering it with drugs rather than lubrication and maybe a bandage soft contact lens—is only going to make it worse."



An early midperipheral contact-lens-related corneal ulcer caused by fluoroquinolone-sensitive *serratia marsescens*.

Taking a Culture

"I never empirically treat a true corneal ulcer or a serious-looking infiltrate without harvesting material for diagnosis," says Dr. Foster. He notes that when culturing a microbial ulcer it's important to include the edges and base of the ulcer, along with any discharge, for smears on glass slides and for plating onto various culture media. "I personally like two split plates, chocolate and blood agar," he says. "You make streaks on each half of both plates; then, keep one at room temperature and put the other in an incubator. This is helpful because the one kept at room temperature will be extremely good for growth of fungi. I'll also plate onto Sabroud's medium for fungus, in addition to something for isolating anaerobic bacteria. Whether that is thioglycolate or another blood plate placed in an anaerobic incubator depends on my location at the time.

"If I'm suspicious that there's a parasite like *acanthamoeba* involved, the process gets even more complex," he continues. "In that situation the material has to be transported in saline and then plated by the microbiologist to a culture plate that's already growing *E. coli.* The most important thing is to make this happen in a timely manner. If necessary, have the patient meet you at the hospital emergency room and do it there, or refer the patient to an eye residency program if there's one nearby. The resident on call can take care of it."

Dr. Sheppard adds that a culture can be taken from the conjunctiva and the cul-de-sac as well. "There's a good chance that the organism growing in the cornea will be found in those locations," he points out. "Also, with a contact lens user, you may be able to culture the infectious organism from the contact lens case, if the patient brings it in."

Dr. Sheppard notes that there are visual and tactile clues that may suggest a particular type of organism when scraping a large ulcer. "With a gram positive organism, you don't see too much tissue necrosis," he says. "Instead, you get a kind of sandy consistency to the ulcerated corneal bed. On the other hand, a gram negative organism will produce a necrotic effect with loss of normal tissue and a lot of necrotic debris, a soupy appearance and mushy feel."

Dr. Foster adds that you should never wait for the test results to begin treatment. "Starting treatment before knowing the results of the test is standard of care," he says.

Dr. Foster notes that clinicians frequently ask whether they should do an anterior chamber tap for a culture when a patient has an ulcer and a hypopyon. "That's a bad idea, because if the ulcer is bacterial, the hypopyon is always sterile, 100 percent of the time," he explains. "Bacteria don't get through an intact cornea. The hypopyon is a reaction, not an infection. But in the course of doing a tap, one may actually drag bacteria into the anterior chamber, inoculating it and risking creating a catastrophic endophthalmitis.

"The only instance in which I'd consider a tap is where we've never isolated the microbe; things are not going well—in fact they're getting worse; there are some features that are making us pretty suspicious of fungus; and the process is getting deeper and deeper. I will do a tap in that situation, because fungus can pass through an intact Descemet's membrane."

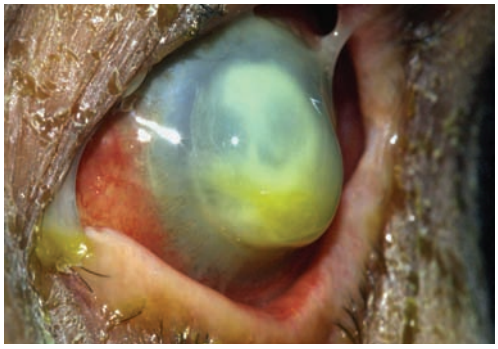
Choosing an Antibiotic

"In ulcer cases where I'm really concerned, I want to use a potent broad-spectrum antibiotic in the fluoroquinolone class," says Dr. Sheppard. "I think the best fluoroquinolone for ulcers right now is besifloxacin, because of its high concentration, its ability to adhere to the surface and its superior MIC values for a wide variety of infectious bacterial organisms, particularly multi-drug resistant *staphylococci*."

Dr. Wittpenn's preferred drug for corneal ulcers at the moment is also besifloxacin. "It has very good coverage from a fluoroquinolone standpoint—it covers both gram positives and gram negatives—and it contains benzalkonium chloride," he explains. "Certain fluoroquinolones like besifloxacin or gatifloxacin, in combination with BAK, remain very effective against methicillin-resistant bacteria such as MRSA, which we're increasingly worried about.

"If a patient comes in with any kind of ulcer that involves an epithelial defect, I prescribe besifloxacin every

hour for the first day," he says. "If you can't get besifloxacin, my second choice would be a fluoroquinolone with BAK such as Zymaxid. If the patient's insurance is generic only, which a lot of plans out there are, the third choice would be ofloxacin, again because it has BAK mixed in. It's not as good as the other two, but may serve if the other options are not possible."



A necrotizing corneal ulcer caused by *pseudomonas*.

If an ulcer is advanced, most surgeons say they'd treat with multiple antibiotics. "When treating a microbial ulcer, a typical treatment is to choose two antibiotic agents and treat aggressively," says Dr. Foster. "By aggressively I mean perhaps six or eight initial drops, one every five minutes, followed by a drop of one of the antibiotics every hour on the hour with a drop of the other antibiotic every hour on the half hour."

Dr. Sheppard concurs. "In more severe cases, I'll use dual therapy with besifloxacin and gentamicin," he says. "Gentamicin is not very soluble, so while the besifloxacin achieves very high concentrations initially, it takes a while for the gentamicin to build up. However, gentamicin is available in injectable vials, so when the patient is in the office I'll give a subconjunctival loading dose injection of 0.3 cc gentamicin mixed with 0.3 cc lidocaine at the time of presentation, along with a drop of besifloxacin. (We don't need to give this fluoroquinolone every five minutes to load the patient because of its superior pharmacokinetics.) That way I know the patient is immediately under treatment. Hopefully, the patient will go to the pharmacy right away and pick up the respective drops and then return to the office in that first critical 24-hour period, so I can see if he's getting better."

Dr. Foster notes that there's some debate regarding whether or not to use so-called compounded fortified antibiotics, typically compounded in the hospital pharmacy. "Studies have indicated that the hourly use of a broad-spectrum fluoroquinolone such as gatifloxacin or moxifloxacin is just as good as, for example, fortified vancomycin and tobramycin," he says.

Dr. John points out that whether or not the epithelium is compromised makes a difference with regard to topical antibiotic penetration into the corneal stroma. "If the epithelium is intact, topical antibiotics have a hard time getting into the cornea," he says. On the other hand, if the ulceration has already removed a piece of the epithelium and part of the stroma, you don't have to worry about the epithelial barrier."

He adds that when the epithelium is intact, the longer an antibiotic stays on the ocular surface the more likely it is to penetrate into the cornea. "Some drugs include an additional component that helps retain the drug on the ocular surface longer, leading to increased contact time," he says. "For example, Besivance contains DuraSite—polycarbophil, edetate disodium dihydrate and sodium chloride."

The Steroid Dilemma

One of the most controversial issues surrounding treatment of corneal ulcers is when—and whether—to treat with corticosteroids.

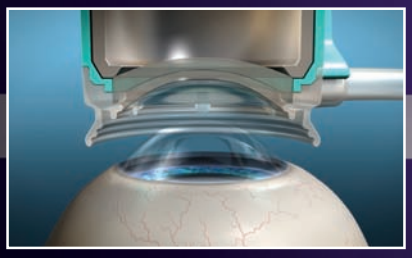
"Corticosteroids are a double-edged sword," says Dr. John. "Once the infection is controlled, steroids can help decrease the scarring that can result from the infectious process. However, when there's an active infection you don't want to use steroids because they'll frequently have a deleterious effect. But that is often a million-dollar question: How can you be certain the cornea is sterile?

"The SCUT study (Steroids for Corneal Ulcers Trial), a large series involving 500 patients that was published in the *Archives of Ophthalmology*, found no overall difference in three-month BSCVA and no safety concerns with adjunctive corticosteroid therapy for bacterial corneal ulcers," he continues. "But I usually avoid steroids when an infectious process is there. I would only use it when I believe the infection is completely under control, because you're cutting down the cornea's host defenses against the enemy and they can help the organisms proliferate."

Dr. Sheppard agrees that corticosteroids can be useful, but only in specific circumstances. "I believe a classic gram positive infection will benefit from initial steroid therapy," he says. "Recent data from the Proctor Foundation tells us that there may be an improved visual prognosis—but only for central ulcers when steroids are prescribed initially—and that the steroids have no significant unexpected deleterious effects [in this situation]. On the other hand, if the patient has a fungal infection, giving a steroid is the worst thing you can do. No patient with trauma should get a topical steroid because the risk of a fungal infection is much higher."

Dr. Foster believes that if you're sure a microbe is being effectively treated with the chosen antibiotic, a judicious use of steroid to reduce post-inflammatory response damage to the cornea is perfectly acceptable. "In this situation, where you have a significant level of comfort that you're on top of this, if there is significant inflammation that you'd like to blunt, I believe most corneal disease experts would

Smarter, Better, Faster.[1]
Advancing Every Femtosecond.



INTRODUCING THE NEW

LenSx® SoftFit™ Patient Interface

SMARTER
- Enhances patient comfort
- Minimizes corneal compression
- Fixates cornea for precise incisions

BETTER
- Free-floating capsulotomies in nearly every case
- Pristine capsulotomy edges
- Lower IOP rise of only 16 mmHg during the procedure
- Less energy required

FASTER
- Reduction in laser time with overall reduction in procedure time
- Simpler, easier docking process

1. Multicenter prospective clinical study (n=197 eyes); Alcon data on file.

Alcon®

a Novartis company

Designed for Growth™

LenSx® LASER

LenSxLasers.com

agree that stepping in with a little bit of steroid is reasonable," he says. "I'm not saying it's standard of care, but it's reasonable."

Dr. Wittpenn, however, feels that steroids are never a good choice when treating an infectious ulcer. "I find that steroids will get you in trouble faster than they'll get you out of trouble," he says. "The only time I'd use steroids is in a case like a phlyctenular keratitis, which is not infectious. Steroids have never been shown to decrease scarring. It's tempting to use them because they'll help the patient feel better, at least transiently, and the eye gets white faster. However, steroids can mask a lot of things.

"One patient was referred to me because she got a scratch working in the garden," he continues. "She was treated by her local eye-care provider, who thought it might be bacterial and treated accordingly; however, it never got completely better. She still had some anterior chamber reaction, and the epithelium developed a funny appearance where it had partially healed. The doctor thought the trauma must have induced a herpetic keratitis, so he added an antiviral. But he still saw inflammation in the anterior chamber, so he also added a steroid.

"She was treated with the steroid and antiviral for about three weeks before she was finally referred to me because the ulcer wasn't getting better," he says. "By then she had started to develop a fungal ball in the deep stroma, and it ultimately broke through into the anterior chamber. At that point we did a tap of the anterior chamber and found that she had *Aspergillus niger*. It was difficult to treat. It took months, including 17 intracameral injections of an antifungal, amphotericin, which of course had to be specially prepared. She ultimately needed a transplant and cataract surgery. In the long run she did well—but the steroids certainly made the case much more difficult to treat.

"So I tell colleagues, if you're dealing with what you believe is an infectious ulcer, you have to be very comfortable with what you're doing before you add a steroid," he concludes. "That's probably the number one mistake I see clinicians make."

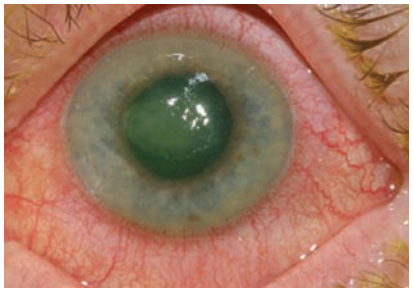
Dr. John notes that you should also remember your treatment priorities. "Steroids may help to decrease scarring," he says, "but if you have a bad corneal ulcer, the number one priority is to try to get rid of the offending organisms and minimize the overall direct and collateral damage to the cornea. In the best possible scenario, steroids might decrease the subsequent scar formation, but even if you use them you're often not going to eliminate the scar."

Fungal Ulcers

"Fungus is suggested as the cause of an ulcer when the history reveals that the ulcer is not becoming rapidly fulminant," Dr. Wittpenn says. "It's not developing a dense infiltrate quickly, and it's not responding to antibiotics that are being used appropriately. Another clue that fungus may be involved is if the source of an abrasion was a scratch from vegetable matter such as branches or plants. At least up here on Long Island, the vast majority of fungal infections I take care of have that history; it may be a little different in the south where fungal infections are more common."

"Fungal ulcers are often diagnosed late, because unless there's an obvious cause we generally begin by assuming that patients have a bacterial keratitis," notes Dr. Sheppard. "Fungal ulcers tend to be caused by trauma, but if the patient has a compromised surface, loves gardening, already had a corneal transplant or there's a foreign body in the eye, all bets are off.

"You have to look at the physical appearance," he adds. "A fungal ulcer tends to have very fuzzy margins, tends



A neurotrophic keratitis caused by a long-standing herpes simplex virus infection. This eye is at a high risk for secondary bacterial colonization and infection.

to be deeper and tends to present with a plaque on the endothelium; it may have a delayed onset, and may have multiple foci. These clues can help us decide where we rank the probability of a fungal cause for the ulcer."

Dr. Wittpenn says he uses several approaches to address a fungal ulcer. "Suppose a patient comes in with what appears to be a bacterial ulcer," he says. "It's been treated properly, let's say with tobramycin every two hours, but it's not getting better or worse. The first thing I'd do is add a fortified vancomycin because the treatment so far hasn't really covered gram positive bacteria that well; I'd also switch the patient to a fluoroquinolone.

"At this point I'd give the patient two or three days to see if he improves," he says. "The best way to determine that is by the reported level of pain dropping, and by checking the peripheral cornea, which will clear first. That will indicate that you're no longer recruiting white cells, and that's usually a sign that you've found the correct treatment. You can't judge by the infiltrate, because the infiltrate will get denser at first; it will begin to heal as the white cells consolidate. If there's no improvement on the antibiotics after three or four days, I'll have the patient stop the drops for 24 hours and then culture for fungus. Occasionally, depending how bad the ulcer is and how long it's been there, I'll begin to treat with an antifungal like natamycin even pending the fungal cultures."

Dr. John notes that even when the patient's history gives you a high index of suspicion that the infection is fungal, you should treat for potential bacterial infection at the outset. "Treat with antibacterials and do the cultures to prove that it is fungal," he says. "Antifungal treatments can often be toxic to the ocular surface. In this scenario you're going to treat very intensively, so you want to have a definitive diagnosis before you start treating with those agents—although of course there can be some exceptions, depending on the clinical setting. Besides, even if fungus is present, you can also have a bacterial presence."

He adds that it's also important to know what kind of fungus you're dealing with. "Is it *Candida* or is it a filamentous fungi like *Fusarium*? That also can help you decide what type of antifungal treatment to initiate," he says. "You can change your treatment direction or add antifungal agents once you have a definitive diagnosis, either by smear, culture or biopsy."

Monitoring Progress

"Once you start treatment with antibiotics, you have to monitor the corneal infection closely," says Dr. John. "When you do cultures, you get a report identifying the organism and a report telling you whether the organism is sensitive to the antibiotic or resistant, but the single most important factor is the clinical response to treatment. If you're treating a bad corneal ulcer and you see that the infiltrate size is getting smaller, the ulceration is not getting worse and there is evidence of healing taking place, especially in the periphery, then of course you want to continue with the same treatment modality. On the other hand, if you're treating aggressively with an antibiotic and the ulcer is getting worse, you have to change direction or add additional antibiotics."

Dr. John points out that bacterial organisms are very adaptable. "They become resistant to antibiotics," he says. "It's a constant battle to keep ahead of them. So you have to monitor very closely to see if your ocular antibiotic choices are working from a clinical standpoint."

If medical treatment fails to work, surgery may become necessary. "You don't want to wait too long for surgical intervention when there is an expanding ulcer with medical therapeutic failure," notes Dr. John, adding that the clinical response is dependent partly upon the location of the ulcer. "For instance, if you have a *Pseudomonas* ulcer that is paracentral and is expanding rapidly despite medical treatment and moving towards the limbus, you may have to consider surgical intervention such as a therapeutic keratoplasty. If that infection spreads from the cornea to the sclera, resulting in *Pseudomonas aeruginosa* keratoscleritis, then the odds of saving the eye as a whole can rapidly diminish. Even in cases where evisceration or enucleation are not necessary, the visual prognosis usually remains poor."

On the other hand, if the treatment is working, the clinician has to decide when to taper the medications. "If the infiltrate is decreasing, the pain is decreasing, the redness is decreasing and the epithelial defect is improving, then I know that the patient is responding to therapy," says Dr. Sheppard. "Once all of the symptoms are gone and the epithelium is completely resurfaced, I feel safe in concluding that we've eliminated the bacteria, and we can begin to rapidly wean the patient off the antimicrobial therapy. Sometimes, because of the toxicity that comes with any potent antibiotic given frequently, we cut back on the dosage frequency once we see improvement—assuming that the information from the cultures also indicated that the current therapeutic regimen is the right one.

Finally, we watch the patient for about a week after we stop the antibiotics to make sure the cornea remains clear without therapy."

Clinical Pearls

These strategies can help you avoid common mistakes that might undercut the effectiveness of your treatment:

• ***Don't confuse an infiltrate with an ulcer.*** Dr. Foster notes that an infiltrate, by itself, is not synonymous with a corneal ulcer. "A corneal infiltrate indicates that some white blood cells have migrated into the corneal stroma, but that doesn't mean an ulcer is present," he explains. "In a true ulcer, there's a loss of tissue with stroma digested by enzymes. The result is a divot, just like an ulcer in the lining of the stomach. An infiltrate is of concern because it can eventuate into loss of tissue—hence, an ulcer—but it's important to make the distinction.

"If you have a peripheral infiltrate in a contact lens wearer, with no loss of stroma, no real ulceration and an intact epithelium, stop the contact lens use, use a topical combination of antibiotic and steroid and see the patient frequently," he continues. "I'd see the patient the next day, and if he looks good, see him two days later, then four days later, and so forth."

• ***Beware of undertreating a contact lens-related ulcer.*** "Sometimes a contact lens patient comes in so early that you don't even see a big infiltrate," notes Dr. Wittpenn. "I always warn people about a patient who says, 'I think I scratched my eye when I took out my contact lens last night, because I woke up this morning and it was real sore and bothering me.' All you see is a corneal defect—no infiltrate. In this situation you need to be alert for any cells in the anterior chamber and any kind of haze at all.

"My advice to most clinicians is: Any corneal defect in the setting of contact lens use is a corneal ulcer until proven otherwise," he continues. "The biggest error clinicians make in this situation is prescribing an antibiotic twice or four times a day. When you hit the ulcer with a low dose like that—particularly if you're using one of the very popular antibiotics like tobramycin or gentamicin—treatment might be effective, but those drugs have gaps in their coverage. Three days later the area still isn't really healed in; it's more inflamed, and now you're not sure if you're dealing with an unusual fungal ulcer or something else. Doctors end up sending these patients to me to rule out fungus, when in fact it's an undertreated bacterial ulcer that just needs

to be hit hard with topical antibiotics.

"A central contact-lens-associated ulcer can have devastating effects on vision, and develop very quickly, within 24 hours," he adds. "That's why any problem associated with a contact lens should be treated aggressively. If it really is nothing but a defect, nothing is lost. If it's the start of an infection, you may save the patient's vision."

• ***When choosing an antibiotic, always consider avoiding those the patient may have used previously.*** "If the patient has had a particular antibiotic such as azithromycin or Ocuflox in the past because of cataract surgery or a bout of conjunctivitis, you may not want to treat the ulcer with those medications—particularly if the patient may have abused them by not using them for the full course of therapy," observes Dr. Sheppard. "Instead, if the ulcer is serious, pick a very potent, broad-spectrum antibiotic, especially if you're selecting monotherapy. If you're using multiple drugs, select a strategy that will cover the broadest range of potential pathogens."

• ***Be alert for a shield ulcer.*** "One form of ulcer that's been a little more prevalent recently is a shield ulcer, which is associated with severe allergic conjunctivitis, commonly seen in teenage males, though it can also be seen in young adult males," says Dr. Wittpenn. "They get such a severe allergic reaction and inflammation under their upper lids that the epithelium of the cornea breaks down in response to the inflammatory papillae that form, which become big bumps that can cause an ulcer. The real problem occurs if that ulcer becomes secondarily infected.

"Patients in this situation need to be managed carefully," he continues. "They often need to be treated with a topical steroid in conjunction with an antibiotic. Unless you're comfortable handling this type of ulcer because you've taken care of a lot of them, you really should send this patient to a

specialist. These patients can get into trouble quickly, particularly if they get an infectious ulcer centrally; suddenly you're dealing with a bad scar and a patient who might be fairly young but needs a corneal transplant."

• ***Warn patients about secondary fungal infections.*** "Many times you treat a bacterial infection with antibiotics and the bacterial infection gets better," says Dr. Sheppard. "Then the patient is running around in the garden or working in the basement or attic or playing with a pet and gets a fungus in the eye. Fungus will grow more rapidly in an eye with antibiotics on board, because suppressing the bacterial growth allows fungi to grow faster. As a result, we've often seen secondary fungal infections. It's worth mentioning this to the patient."

• ***Tell contact lens patients that they need to have a pair of spectacles in reserve.*** "Contact lens wearers often reject this idea," notes Dr. Wittpenn. "They say, 'I wear my lenses all the time.' I tell them that they have to understand that if a contact lens starts to bother them, they have to be able to remove it and wear glasses until the problem is resolved. I've seen people get themselves in trouble because they had no spectacles to fall back on."

• ***Be careful about diagnosing an infection as being herpes-based.*** "It's possible to misdiagnose an infection as a herpes infection, leading to treatment using antiviral agents," says Dr. John. "In fact, that early dendrite-like lesion that you see may be a radial keratoneuritis or an early epithelial ridge-like lesion secondary to *Acanthamoeba* keratitis. That misdiagnosis could delay the treatment of *Acanthamoeba* and have a deleterious effect on the patient's vision."

• ***Don't be afraid to hospitalize a patient.*** "You have to consider the possibility that compliance is an issue, especially if the ulcer is getting worse in spite of your having prescribed what you think is the state-of-the-art treatment for the given problem," says Dr. John. "Putting the patient in the hospital may be a good alternative if the patient is noncompliant, because time is of the essence, especially if you're dealing with an organism like *Pseudomonas*. You can tell the patient that he won't be in the hospital for too long; he'll be discharged as soon as the ulcer begins to get better and he can manage the treatment at home."

Dr. Foster agrees. "If the patient has a microbial ulceration that needs aggressive treatment, in my experience the vast majority of patients cannot be trusted to get it done," he says. "By far the best solution is to let the nurses do it. Put the patient in the hospital. No insurance company would ever argue about hospitalizing a patient for an infectious corneal ulcer." He adds that this is especially important if the ulcer is central or paracentral.

• ***Don't assume that ongoing corneal opacity means your treatment isn't working.*** Dr. John notes that clinicians may be fooled into overtreating by an ongoing corneal opacity. "A treated ulcer may be under control, but the clinician is concerned about the ongoing corneal opacity," he explains. "This opacity may be the result of the scarring process rather than the infection, but the clinician keeps treating. This can lead to surface issues such as toxicity from the drugs and a corneal surface breakdown. The clinician should be tapering the medication because the infectious process is under control.

Make Sure Your Staff Is Prepared

In the struggle to preserve vision in the face of a corneal ulcer, your staff are the first line of defense; their actions can make or break a positive outcome.

• ***Make sure staff members know when a call might be about a developing corneal ulcer.*** It's often a staff member who fields a patient inquiry related to a corneal ulcer, not the eye-care provider. "The OMIC malpractice insurance company states that the third leading cause of malpractice lawsuits against ophthalmologists is triage by staff members," says John Sheppard, MD, MMSc, professor of ophthalmology, microbiology and molecular biology at Eastern Virginia Medical School in Norfolk, Va. "This means that triage personnel have to be really tuned in to which phone calls are important and what constitutes a potentially blinding condition.

"In a large percentage of these phone calls, it's red eye that we're concerned about," he notes. "If the red eye is of long duration, with no risk factors, no pain or purulent discharge or loss of vision, that's one thing; that's quite common. But whenever the patient's comments indicate a risk factor for bacterial keratitis, such as pain and photophobia in addition to the red eye, especially in conjunction with contact lens wear or trauma, the triage person has to get the patient into the office right away. The last thing you want to do is delay the presentation of an ulcer."

• ***Tell your staff: If a patient might have an ulcer, don't put drops in his eyes.*** "Aside from diluting the flora, most of the eye drops we use to reduce pain, check IOP or dilate the pupils contain a preservative," explains Dr. Sheppard. "The preservative may significantly reduce our chance of culturing an organism from the eye, which ultimately guides our therapy—particularly in difficult cases. Eventually we'll use preservative-free tetracaine to culture and debride the cornea."

• ***Make sure your staff knows that red eye might also indicate adenovirus keratoconjunctivitis.*** "These patients can have symptoms similar to those of an ulcer, but they're extremely contagious," notes Dr. Sheppard. "Fortunately, the AdenoPlus pathogen screener from RPS, distributed by NiCox, allows us to confirm whether or not a patient has this condition within about five minutes, with very high sensitivity and specificity."

—CK

"Signs that your treatment is working despite the opacity include: healed corneal epithelium that was initially broken down; decreasing corneal stroma edema surrounding the area of initial dense infiltrate; and blurry infiltrate margins becoming more distinct," he adds.

• ***Consider using cyanoacrylate glue to forestall a perforation.*** "A perforation is a pretty scary event," notes Dr. Sheppard. "We may put cyanoacrylate glue on a cornea that's thinning, and a small perforation can be glued. A large perforation, unfortunately, is going to require an emergency transplant."

When Should You Refer?

"Any time you're dealing with a type of ulcer you seldom treat, such as a shield ulcer, you should consider referring the patient," says Dr. Wittpenn. "Generally, you have to be very comfortable discerning whether an ulcer is infectious or noninfectious. Also, any ulcer that isn't doing what you expect it to do should be referred. Clinicians have a tendency to say, 'Well this isn't terrible, but it isn't getting better. Maybe if I just give it a little steroid …' Whenever you get the urge to reach for a steroid because you think it will help the eye heal faster, I urge you to resist. That's the main choice that gets clinicians into trouble."

"If you don't actually enjoy managing these kinds of cases, don't try to manage them," adds Dr. Foster. "Just refer the case out to someone who does enjoy this type of case, or to the local residency program." REVIEW

Dr. John is a consultant and speaker for Bausch + Lomb. Dr. Wittpenn has been on the speakers bureau at B+L and Allergan and has received research support from Allergan. Dr. Sheppard is a consultant for RPS, NiCox, Alcon, Merck, Allergan and B+L.

A Cross Section Of Cross-Linking

Walter Bethke, Managing Editor

A look at the various ways to stiffen the cornea and the results they're producing.

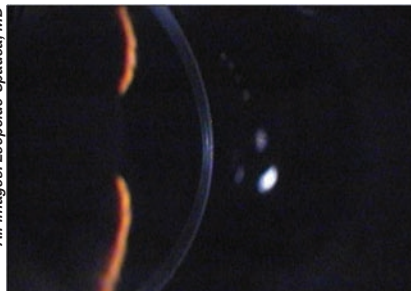
Though it's not approved in the United States, the concept of corneal collagen cross-linking has appealed to surgeons both because of its apparently solid results as well as the myriad ways in which it can be applied: Physicians can use it therapeutically for patients with keratoconus or post-LASIK ectasia, or prophylactically for those undergoing refractive surgery; they can use a longer, traditional method with less intense UV light or a new accelerated approach with greater light; and can choose between cross-linking through the epithelium or after epithelial debridement. Here, experts with thousands of cross-linking cases under their belts help sort out the various approaches, discuss their pros and cons, and share the results they've been able to achieve with them.

Therapeutic Cross-Linking

To get an idea of cross-linking's baseline procedure, the cross-linking approach as originally formulated involves first debriding the epithelium, then instilling 0.1% riboflavin in 20% Dextran over a period of 30 minutes. Then, the riboflavin-laced cornea is irradiated by UV radiation at a power of 3 mW/cm^2 for 30 minutes, while adding a drop of the riboflavin solution every five minutes. Studies have found that this approach arrests the progression of keratoconus in a large majority of eyes, and decreases corneal steepness by as much as 5 D.[1,2] Experts anecdotally estimate that this approach is still used by about half of the practitioners in the world.

However, one of the issues surgeons have with the original cross-linking protocol is that it's time-consuming, requiring an hour per eye to complete. In response, researchers began toying with the idea of accelerated cross-linking.

A popular approach to accelerated cross-linking on the international scene, and which is currently under Food and Drug Administration evaluation in the United States, is the Avedro VibeX/KXL treatment. Bogota, Colombia, surgeon Gustavo Tamayo has performed 1,900 procedures with the system—on both keratoconus



All images: Leopoldo Spadea, MD

The gray demarcation line in the stroma shows the depth of the cross-linking.

and postop ectasia patients—and says he thinks its accelerated approach to cross-linking will become popular.

"I've been using the Avedro system since 2011, but I've been doing cross-linking since 2006, when I started using the German IROC system," Dr. Tamayo says. "I switched to the Avedro system for several reasons. First, it's faster. This system takes six to 10 minutes per eye. Second, it was developed based on a concept with which I heartily agree: You don't need riboflavin anywhere but the first third of the anterior stroma. Going deeper, I feel, doesn't work better and in fact may result in the loss of more keratocytes. Using the IROC system, I started to see a little bit of damage in the posterior third of the stroma in the form of low-grade haze, which resulted in slow visual recovery, some eyes taking longer than six months to get back to their preop BCVA. I believe the reason for the haze was was too much riboflavin in the deeper corneal layers."

Avedro was able to perform adequate cross-linking in less time by modifying both the riboflavin and the energy used. The special riboflavin is called VibeX Rapid, and consists of 0.1% riboflavin without Dextran, to enable rapid uptake. "In addition, they use a high-power UV system," adds Dr. Tamayo. "So, instead of doing 3 mW for 30 minutes, they use 30 mW for three minutes. Ultimately, this higher power for a shorter time ends up delivering the same total power: 90 mW and 5.2 mJ to the cornea."

Though Dr. Tamayo hasn't analyzed all 1,900 patients yet, he can share his overall clinical impressions. "None of the eyes that I've treated with this system has developed any recurrence of the ectasia, and I've been able to stop the progression of the cone in all of them," he avers. "Currently, it's working without the haze, the ulcers or the delay in recovery of vision that I had in some cases with my previous unit. Some patients may have had a delay in re-epithelialization, but no one has lost any lines of best-corrected vision or has lost endothelial cells. However, if someone were to say that two years of follow-up may be too short to say whether a cross-linking system is working or not, I'd have to agree."

In the United States, Avedro is involved with two studies. The first, which is currently in the data-analysis phase, is studying accelerated cross-linking. It compares the procedure to a sham-treatment group. "The early response patterns show a relatively homogeneous and deep cross-linking effect," says Peter Hersh, MD, Avedro's medical monitor. "The eyes show the expected stromal haze and the OCT shows deep demarcation lines, as one would expect after cross-linking."

The second study uses Avedro materials, and is sponsored by the American-European Congress of Ophthalmic Surgery. This study will include as many as 2,000 eyes with keratoconus and 2,000 with postop ectasia, and will randomize them among three groups: 15 mW light; 30 mW light and 45 mW light. The ACOS study's recruitment phase is currently under way.

In terms of selecting patients for cross-linking, surgeons have recently made strides on that count, as well. John Kanellopoulos, MD, a surgeon from Athens, Greece, who has been at the forefront of many advances in cross-linking, says that his group has found that visual acuity and corneal thickness are actually poor indicators of the degree of irregularity in the cornea.[3] "We feel that the data is compelling that corneal regularity indices of the sort provided by many topographic devices are far more sensitive and reliable in picking up the clinical degree of keratoconus and its progression," he says. "In [our] paper, we reviewed over 700 patients through five years of follow-up, and measured all clinical parameters such as UCVA and steepest Ks, as well as eight topometric parameters on the Pentacam. We found that the two most significant red flags for picking up keratoconus or its progression were the index of surface variance and the index of height decentration. Visual acuity was irrelevant. Again, this was in a group of young keratoconus patients, a group that I feel needs the most attention, because older keratoconus patients don't change much."

Cross-Linking Plus PRK

Another wrinkle surgeons have added to cross-linking is the inclusion of simultaneous topography-guided surface ablation. The concept was first introduced by Dr. Kanellopoulos and has become known as the Athens Protocol.

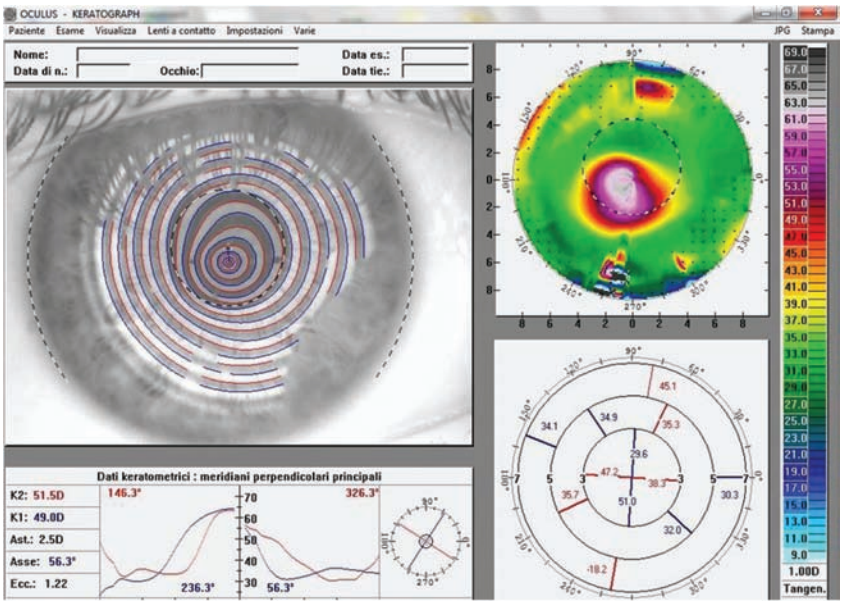
"Though cross-linking has been found to be successful in the literature, the problem is that patients who can't tolerate rigid gas permeable lenses, are still left with an extremely irregular optical system," explains Dr. Kanellopoulos. "So we introduced the concept of using the excimer laser to remove 20 to 30 µm of tissue. At first blush, ablating like this might seem undesirable in a cornea that's already thin, but the advantage is great: Not only does the cornea appear to be stable afterward, but it seems to be far more visually competent."

In a study of the technique in 325 eyes with keratoconus, Dr. Kanellopoulos divided the eyes into two groups: One group (n=127) underwent cross-linking with topo-guided surface ablation done six months later (the sequential group); and the other (n=198) underwent the two procedures at the same sitting (simultaneous group). He says the simultaneous group did statistically significantly better in all measures, including improvement in uncorrected vision (improving from 0.96 ±0.2 to 0.3 ±0.2 logMAR) and best-corrected vision (improving from 0.39 ±0.3 to 0.11 ±0.16 logMAR), the mean reduction in spherical equivalent refraction and keratometry and their level of corneal haze.[4] "The data

is compelling toward the combined procedure having a synergistic effect," says Dr. Kanellopoulos. "But the clinician must be advised that this isn't a PRK treatment. We're not treating refractive error. We're using a minimal, topography-guided PTK, so to speak. This treatment shifts the corneal curvature in order to normalize it. In some cases, in fact, it induces myopia, so we theoretically worsen the refractive error. However, the aim is to increase BCVA—and it invariably improves."

Dr. Kanellopoulos performed a prospective study of 412 Athens protocol patients to analyze the safety of the procedure, as well as to get a sense of cross-linking's complications in general. The complications were as follows:

- 30 percent reported severe pain on day one postop, 25 percent reported moderate pain and 45 percent had no significant pain;
- 75 percent had delayed epithelial healing by day six, and 10 percent had delayed healing by day 10;
- 25 percent had transient epithelial scarring that lasted for a month;
- at six months, 12 cases (2.9 percent) had subepithelial corneal scarring that didn't affect visual function;
- transient stromal haze occurred in 15 percent of cases, but 95 percent of them resolved by month six;
- there were eight cases (1.9 percent) of persistent haze past month six and one case of late stromal haze (0.2 percent) occurring at one year postop with intense sunlight exposure, which subsequently responded to a six-month course of Lotemax; and
- seven (1.6 percent) showed ectatic progression, four of which needed additional cross-linking (0.9 percent).[5]



In this postop ectasia case, cross-linking reduced the power of the ectasia's apex by 3.5 D.

Epi-On vs. Epi-Off

Since performing cross-linking the traditional way involves debriding the epithelium, with its attendant issues as the cornea re-epithelializes, some surgeons have taken to performing cross-linking through the epithelium, leaving it intact. This approach may also help in corneas that are a shade too thin for epi-off, they say. The approach may involve trade-offs, however.

Leopoldo Spadea, MD, associate professor at the University of L'Aquila in Italy, has seven years of experience with epi-off and four years of experience with epi-on treatments, and has discovered some things about them along the way. "Epi-on is a less-invasive technique, with less pain, a faster recovery period and faster healing, but less efficacy," he says.

To promote the penetration of riboflavin, Dr. Spadea says he uses a special formulation called Ricrolin TE (Sooft, Montegiorgio, Italy), which he instills every 10 minutes over a two-hour period. After instilling a topical anesthetic and pilocarpine to constrict the pupil in an effort to prevent UV damage to the lens and retina, he instills five more drops of riboflavin over a 15-minute period. Then, he irradiates the cornea for 30 minutes with 3 mW/cm^2 of radiation, all the while instilling riboflavin at five-minute intervals.

"I've found epi-on's efficacy to be one-fifth of the epi-off technique," he says. "It's a good technique, just less effective. With epi-off, the efficacy is more evident. The demarcation line—a gray line inside the cornea that shows where the radiation treatment has reached—is very deep with epi-off, but with epi-on it's very superficial. With epi-on I can obtain an average reduction of the apex of the cone of around 1.5 D, sometimes as much as 2 D. With the epi-off technique, the reduction of the apex of the cone is between 4 and 5 D, and these results are more consistent and easier to obtain.

"I have had some patients in whom one cornea was thicker than the other," Dr. Spadea continues. "In the thinner cornea we performed the epi-on technique; with the thicker, the epi-off. The refractive result was more evident in the epi-off technique, with an increase in both BCVA and UCVA."

Dr. Spadea says the best candidate for epi-on in his practice is someone in whom the cornea is less than 400 µm. "That's the most important indication for me," he says. "It also makes it easier to perform cross-linking on children. However, in an older, cooperative patient in whom the cornea is greater than 400 µm, for me, currently, the

BEST HOSPITALS
U.S.News & WORLD REPORT
HONOR ROLL
2013-14

WE'RE CHANGING THE WAY

PATIENTS WITH VISION IMPAIRMENT ENVISION THEIR FUTURE

The Louis J. Fox Center for Vision Restoration of UPMC and the University of Pittsburgh—a joint program of the UPMC Eye Center and the McGowan Institute for Regenerative Medicine—is the first national, comprehensive, and multidisciplinary research and clinical program dedicated to ocular regenerative medicine. Our ophthalmologists and researchers focus on the discovery of new treatments for blindness and impairment through tissue regeneration, enhancement, transplantation, and technology. We're working hard to improve the quality of life for the millions of people affected by vision loss, so that we can all see a brighter future. Learn more at **UPMCPhysicianResources.com/Vision.**

UPMC LIFE CHANGING MEDICINE

UPMC is affiliated with the University of Pittsburgh School of Medicine.

epi-off technique is better."

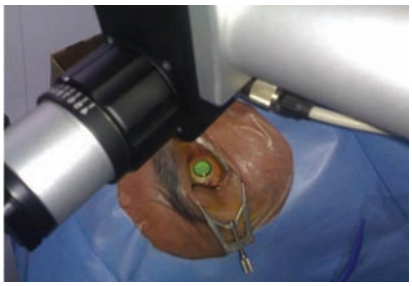
The multicenter CXL-USA cross-linking study has made epi-on cross-linking its procedure of choice for FDA trials, and its investigators have reported good efficacy. In its study of 181 patients who underwent epi-on cross-linking, the average cylinder decreased from 4.52 to 3.96 D. Also, the average 2-mm K astigmatism on Pentacam decreased from 5.47 to 4.66. Forty-six percent of the eyes gained one or more lines and 36 percent had no change in their BCVA. Thirty percent lost one or more lines. The average follow-up was 10.9 months. (*Rubinfeld R, et al. IOVS 2012;53:ARVO E-Abstract 6786*)

Cross-Linking Plus LASIK

As a hedge against possible ectasia, some surgeons are adding a cross-linking treatment to their LASIKs.

Dr. Tamayo says that when used with the Avedro system, this approach is known as LASIK Xtra. "When you create a flap with LASIK, studies have shown that you decrease the biomechanical strength of the cornea, even if you don't perform the ablation," he says. "I thought it would be good to have a procedure with fast visual recovery like LASIK that didn't reduce the cornea's strength, so when I heard about LASIK Xtra, I was interested. To perform the procedure, you perform the LASIK, then instill Avedro's VibeX Xtra riboflavin, which is 0.25% and has no Dextran, to the bed for a minute and 15 seconds. Then, you replace the flap and irradiate the cornea for another minute and 15 seconds."

Before he adopted the procedure, though, Dr. Tamayo wanted to make sure the cross-linking didn't interfere with the LASIK, so he conducted a study in which he performed LASIK Xtra in one group of patients and LASIK in another group. "At one month, my results were the same," he says. "There were no changes in UCVA or BCVA. Since it didn't change the LASIK, I developed some indications for it, all for patients with normal corneas: The first is young patients, 21 to 23 years old. The next is for patients who are heavy eye-rubbers. And third, I will use it in high myopes. In these patients, even though they have normal corneas, the fact that I did a large, deep ablation in addition to creating a flap, I see no reason not to use cross-linking for them. I must note, though, that LASIK Xtra isn't intended for patients at high risk for developing ectasia. In such cases, I think the surgeon should choose a procedure without a flap." Dr. Hersh says that Avedro plans to launch a U.S. clinical study of LASIK Xtra combined with hyperopic LASIK for patients with +2 to +6 D of hyperopia late in 2013.



In epi-on cross-linking, special riboflavin is used to penetrate the epithelium quickly.

Cross-Linking in Children

Surgeons say that, even though very long-term data is lacking, cross-linking appears to be a helpful treatment for young patients with keratoconus when preceded by appropriate discussions with the patient and the parents.

A two-year study from Europe composed of 48 eyes of patients aged 4 to 18 (mean: 13.7) found that the patients' logMAR UCVA improved significantly, from 0.81 to 0.61 ($p<0.05$), and their BCVA improved from 0.43 to 0.21 ($p<0.05$). Topography showed a statistically significant reduction of mean simulated K in the flat meridian from 46.35 to 45.28 D ($p<0.05$). The researchers say that these positive results are promising for pediatric patients, since they are the group that endures the most dramatic keratoconus progression if left untreated. *(Epstein D, et al. IOVS 2013;54:ARVO E-Abstract 5267)*

When faced with a pediatric keratoconus patient who might benefit from cross-linking, Dr. Tamayo says, "The first thing I tell the parents is that it may not work." He then briefs them on the possible pitfalls. "First, if the cone developed due to heavy eye rubbing in a 7-year-old, for instance, which is the youngest patient I've done cross-linking on, and the rubbing continues, even cross-linking may not stop the damage," he says. "Second, the patient and parents should know that there's a large possibility of having to repeat the procedure again in six or seven years. Third, I inform them that I'm not doing a refractive correction, so the patient may still need glasses or contact lenses afterward." He says the 7-year-old, whose mother had undergone bilateral corneal transplants due to keratoconus, is stable at two years.

As far as age limits, Dr. Tamayo thinks 6 might be the youngest age possible for cross-linking simply due to the ability to successfully analyze a child of that age with elevation topography. He says most of his pediatric patients are between 12 and 16. "That's the time when I, the parents and the patient start to see the astigmatism increase almost every six months," Dr. Tamayo says. "We can see the cone developing, so that's when I go to cross-linking right away." REVIEW

1. Coskunseven E, Jankov MR, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. J Refract Surg 2009;25:4:371-6.
2. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: Long-term results. J Cataract Refract Surg 2008;34:5:796-801.
3. Anastasios JK, Asimellis G. Comparison of Placido disc and Scheimpflug image-derived topography-guided excimer laser surface normalization combined with higher fluence CXL: The Athens Protocol, in progressive keratoconus. Clin Ophthalmol 2013;7:1385-96. Epub 2013 Jul 18.
4. Kanellopoulos AJ. Comparison of sequential vs. same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. J Refract Surg 2009;25:9:S812-8.
5. Kanellopoulos AJ, Cho MY. Complications with the use of collagen cross-linking. In: Agarwal A, Jacob S, ed. Complications in Ocular Surgery. Thorofare, N.J.: Slack, 2013. 115-20.

Invest In Your Practice And Get A Guaranteed Positive Return.

Lombart's CS-4 Package Offers Quality, Style & Value.

Ask about optional Slit Lamp & Chart Projector configurations.

$13,595

Or lease for $269/mo. for 60 months *

Package includes:

- The Lombart CS-4 Chair & Stand
- Topcon VT-10 Refractor
- Topcon SL-2G Slit Lamp
- Reichert LongLife Chart Projector with mount, slide & screen
- Upgrade to the Lombart CVSi21 for only $2000 more or to the CVS-PC for only $1500 more — Additional upgrades & configurations available.

(1-800-566-2278)

Call 1-800-Lombart

Or Your Local Lombart Representative.

Corporate Office - 5358 Robin Hood Road, Norfolk, VA 23513-2430
757-853-8888 | FAX 757-855-1232 | 800-566-2278 | 800-446-8092
www.lombartinstrument.com

ATLANTA•BALTIMORE/WASHINGTON D.C.•BOSTON•BOYNTON BEACH/MIAMI•BRADENTON•CHARLOTTE
CHICAGO•CINCINNATI•DALLAS•DENVER•DETROIT•GREENSBORO•HOUSTON•KANSAS CITY•KNOXVILLE•LOS ANGELES
MILWAUKEE•MINNEAPOLIS•NEW JERSEY/NEW YORK•NORFOLK•PORTLAND•SACRAMENTO•SAN DIEGO•SAN FRANCISCO

***Lease rate subject to credit approval, 1st payment is paid for by leasing company at signing with 59 remaining rental payments of $269 and a $1.00 purchase option. Taxes, freight and installation additional. Hand Instruments optional. Quantities limited. Subject to change without notice.**

Blepharitis: The Cause Guides the Treatment

Michelle Stephenson, Contributing Editor

Some tried-and-true and some new treatment options for this chronic disease.

Blepharitis is typically classified as anterior or posterior, and it has many causes. While anterior blepharitis is curable, posterior blepharitis is a chronic, incurable disease.

"If you don't know the cause, you don't know how to treat," according to Scheffer C. G. Tseng, MD, PhD, Medical Director of the Ocular Surface Center in Miami. "Blepharitis is characterized by inflammation of the eyelids, but we do not know with certainty what actually causes this inflammation. Is the cause of blepharitis purely infectious, purely inflammatory or a combination of both? If it is caused by infection, is it bacteria, fungi or parasites? These questions have not been well resolved in the literature, as no definitive study has clearly separated the relative contribution of these diverse causes. How we differentiate infectious from inflammatory processes remains a clinical challenge."

Anterior Blepharitis

Anterior blepharitis is most commonly caused by a staphylococcal infection of the lid margin. "Golden crusting is pretty typical. Sometimes, the ophthalmologist will perform a culture just to confirm it because, occasionally, there will be multi-antibiotic-resistant staph," says Stephen C. Pflugfelder, MD, from Baylor College of Medicine in Houston.

Blepharitis caused by bacteria is typically treated with a topical antibiotic, either a drop or an ointment that is put on the lid.

Another cause of anterior blepharitis is a mite called Demodex. "The classic signs of this are cylindrical sleeves on the lashes," Dr. Pflugfelder says. "Demodex is diagnosed by pulling out a couple of lashes and examining them under the microscope for the presence of mites. The treatment for Demodex is usually tea tree oil. There is now commercial tea tree oil on a moistened swab called Cliradex."

Recently, Dr. Tseng conducted a study to determine whether there was a relationship between mites and bacteria.[1] A previous study had described a *bacillus* bacterium found in the intestine of the mites and explained how this bacterium might play a key role in causing inflammation in rosacea patients.[2]

Dr. Tseng's study concluded that rosacea blepharitis is highly associated with Demodex mite infestation and the presence of autoantibodies against this *bacillus* bacterium's proteins in the serum of these blepharitis patients. "Therefore, one cannot rule out that the inflammatory response noted in blepharitis patients might well be com-

This article has no commercial sponsorship.

ing from the symbiotic bacteria inside of a parasite," he says. "Because of the hidden nature of these bacteria, antibiotics alone might not be sufficient and effective. That is why we also need to consider lid hygiene, especially the inclusion of an effective agent, such as Cliradex, as a new strategy of reducing Demodex infestation in managing blepharitis."

Another type of anterior blepharitis is seborrheic blepharitis. People with this condition have evidence of flaking in their eyebrows or in their lashes. "Treatment is usually mechanical scrubs and anti-seborrheic shampoos," Dr. Pflugfelder says.

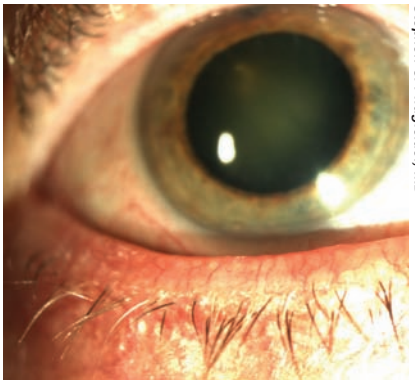
According to Rick Fraunfelder, MD, MBA, from Oregon Health and Science University in Portland, there is also a type of blepharitis called angular blepharitis, in which the patient gets a crusting and inflammation of the angles of the eyelids temporally. "That's usually infectious in nature as well," he says.

Posterior Blepharitis

By far, the most common type of blepharitis is posterior blepharitis, or meibomian gland disease. Treatment for posterior blepharitis varies from just warm moist compresses and massage to oral doxycycline or tetracycline antibiotics, oral nutritional supplements with fish oil and other anti-inflammatory polyunsaturated fats. "There are some topical treatments, too, including topical steroids and topical azithromycin," Dr. Pflugfelder says. "Usually, I start treatment with orals, such as a low-dose oral doxycycline and a nutritional supplement. I use one that has fish oil and gamma linoleic acid. If those don't work, I will add topical steroids or topical azithromycin."

Blepharitis Treatment

The Tear Film and Ocular Surface Society International Report on Meibomian Gland Dysfunction provides the definition, classification, diagnostic criteria and suggested therapies for each type and stage of blepharitis.[3] Marguerite McDonald, MD, from Ophthalmic Consultants of Long Island in New York, says that her current treatment algorithm closely reflects their recommendations as well as her own clinical experience.



Stephen C. Pflugfelder, MD

Figure 1. Meibomian gland dysfunction.

Her basic treatment for mild, stage 1 blepharitis is hot soaks and scrubs. "First, the patient applies two minutes of a wet, warm washcloth over closed eyes to loosen all the lid scurf and to mobilize the altered meibum," says Dr. McDonald. "After the hot soaks, the scrubs are done with over-the-counter eyelid cleansing pads, such as the Ocusoft pads. There is a specific technique for effective lid scrubs. If you don't show people how to scrub their lids, they will do it incorrectly; the devil is in the details."

If a patient has extremely mild meibomian gland disease, then hot soaks and scrubs are all she recommends. If patients have mild-to-moderate disease, she adds AzaSite rubbed into the lid margins twice a day, which is an off-label use. "Patients put one drop of AzaSite on one index finger, rub it between both index fingers, and then rub it on the four lid margins, where the eyelashes dive into the skin on the top of the eyelid wall," she says.

AzaSite can be expensive on some insurance plans, however, and some patients have arthritis or are not coordinated enough to use it. If cost is an issue, or if they sleep with their eyes open, she recommends erythromycin ointment at night instead of Azasite twice a day. "Patients need to apply this ointment immediately before they go to sleep because it can cause blurry vision. I instruct the patients that they should apply more if they get up in the middle of the night. Erythromycin ointment is generic, and it is covered by every insurance plan," she adds.

If patients have moderate-to-advanced dry eye, she prescribes doxycycline 50 mg by mouth each day (more severe cases require it twice a day) for at least six months. Ophthalmologists can also write a prescription for an Ocudox kit, which contains a supply of eyelid cleansing pads as well as doxycycline 50 mg tablets. "Patients must be warned that, even at this low dose, oral doxycycline increases their sensitivity to the sun, so they should wear a hat, a shirt and sunblock when they are outside," says Dr. McDonald. "They also shouldn't take doxycycline one hour before or after a meal containing dairy products because dairy inactivates it."

Blepharitis and Dry Eye

Dr. McDonald notes that blepharitis causes or greatly exacerbates most cases of dry eye, and these two diagnoses are frequently found in the same patients. So, because blepharitis patients often also have dry eye, they are also often on artificial tears and Restasis. "Starting at stage 1, I start the patients on omega-3 nutritional supplements, as there is now much evidence to suggest that omega-3s help in the treatment of dry eyes and blepharitis," she says. "My favorite formulation is Tozal because it is by prescription, it is usually covered by insurance, and it is extremely pure (i.e., all of the mercury has been removed). Tozal also contains lutein and zeaxanthin, which

have been shown to offer a clinically significant degree of protection against age-related macular degeneration. It is the formula that NASA developed for the astronauts in the space station, so it has a great pedigree. Another benefit is that Tozal capsules are smaller than virtually all of the other omega-3 soft gels."

For the mild–to-moderate dry eye that almost always accompanies blepharitis, she recommends Fresh Kote, which until recently was the only artificial tear in the United States that was by prescription and covered by insurance. "Fresh Kote has all three layers of the natural tear film," she says. "If it's not on patients' plans or if the copay is too high, then we advocate Blink, Optive and/or Systane Balance."

When a patient reaches a tear osmolarity score of 317 mOsm/L, Dr. McDonald adds Restasis drops twice a day, accompanied by a quick-tapering dose of Lotemax gel (except for steroid responders or glaucoma patients). She prescribes Lotemax gel four times a day for two weeks, then twice a day for two weeks, after which they stop. "Lotemax gel does two things: the steroid masks the sting that often accompanies the first few weeks of Restasis therapy, and it also provides immediate symptomatic relief," she says. "Restasis takes about a month to kick in, during which time many patients get discouraged and stop using it without a few weeks of a mild topical steroid such as Lotemax gel."

When patients reach a tear osmolarity score of 325 mOsm/L or higher, she does not advocate Fresh Kote or any of the other bottled tears. She switches these patients to unit-dose, preservative-free artificial tears, at least until their tear osmolarity score drops below 325 mOsm/L.

Lipiflow and IPL

These treatment regimens for blepharitis are time-consuming. For patients who are doing everything right but are still suffering, or for patients who cannot do the regimen or who do not want to do the regimen, Lipiflow can be offered.

Lipiflow is a 12-minute, pulsating thermal lid massage that feels like a spa treatment, according to Dr. McDonald. "It allows patients to feel a lot better for about a year, while they are doing much less of the regimen that they hate," she adds.

At the beginning of the procedure, eye cups are placed over the patient's eyelids. During the first two minutes of the treatment, the lids are gently warmed. "Then, gentle pulsations start, and all of their 'eyelid goo' is expelled into the eyecup," she says. "The eyecups are removed after 12 minutes and are thrown away; they are never used for another patient. I tell the patients that they will feel better immediately and will get a little bit better every day for six months, at which point they will reach the maximum benefit from that one 12-minute treatment. They will hold the benefit for nine to 12 months on average, with a range of six to 36 months."

Other ophthalmologists are achieving similar results. A recent study conducted at the Massachusetts Eye and Ear Infirmary found that a single 12-minute treatment with the Lipiflow system offers an effective treatment for evaporative dry eye and meibomian gland dysfunction resulting in a significant and sustained improvement in signs and symptoms for up to one year.[4] The study included 18 patients who underwent Lipiflow and then were able to be followed for one year. Both eyes of each patient were treated, and meibomian gland function, tear breakup time and dry-eye symptoms were measured.

There was a significant improvement in meibomian gland secretion scores from baseline measurements to one-month post-treatment that was maintained at one year. Additionally, tear breakup time was significantly increased from baseline to one month, but this improvement was not maintained at one year. However, the significant improvement in symptom scores on the Ocular Surface Disease Index and the Standard Patient Evaluation of Eye Dryness questionnaire seen at one month was maintained at one year.

Dr. McDonald has not yet had a patient who required a repeat treatment in less than one year. Patients are given instructions about what to cut from their treatment regimen (and in what order) as they begin to feel better. "They remove one item from their regimen each month," she says. "We tell them that there is patient-to-patient variability in how much they can 'jettison' from their routine, so if they begin to feel poorly, they should add back the last item they discontinued."

Dr. McDonald sees the Lipiflow technology as a wonderful addition to her practice. "Like anything else, one must set the patients' expectations properly," she says. "Ophthalmologists make about as much money from Lipiflow treatments as they do from LASIK. There is strong science behind the procedure, patients are happy, and there is virtually no liability."

According to Dr. Fraunfelder, a treatment called intense pulsed light has also been used to treat blepharitis. "It is a laser treatment to heat up the meibomian glands," he says. "The IPL closes down the irregular blood vessels on the eyelid margin, which are called telangiectasias. IPL is a little more uncomfortable than just light and heat." REVIEW

1. Li J, O'Reilly N, Sheha H, Katz R, Raju VK, Kavanagh K, Tseng SCG. Correlation between ocular demodex infestation and serum immunoreactivity to bacillus proteins in patients with facial rosacea. Ophthalmology 2010;117:870-877.
2. O'Reilly N, Menezes N, Kavanagh K. Positive correlation between serum immunoreactivity to Demodex-associated Bacillus proteins and erythematotelangiectatic rosacea. Br J Dermatol 2012;167(5):1032-1036.
3. Asbell PA, Stapleton FJ, Wickstrom K, et al. The international workshop on meibomian gland dysfunction: Report of the clinical trials subcommittee. Invest Ophthalmol Vis Sci 2011;52(4):2065-2085.
4. Greiner JV. Long-term (12-month) improvement in meibomian gland function and reduced dry eye symptoms with a single thermal pulsation treatment. Clin Experiment Ophthalmol 2013;41(6):524-530.

All Pupil II

Vantage Plus

Spectra Iris

Vantage Plus
Digital

Get a
Free Keeler Indirect
When You
Buy Any 3 Keeler Indirects,
& Trade-In Any 3 Indirects
through December 31, 2013

Learn more at www.keelerusa.com

For years, we've been telling you that Keeler* is the world leader in innovation, technology, and market share.

- *First Wireless Indirect*
- *First LED indirect*
- *First Digital Indirect*
- *First Intelligent Optical System*
- *Patented Hi-Mag Lens*

Buy Online!
keelerusa.com

Keeler
OPTICS

*iData Research Inc. 2011 – "Keeler Instruments was the leading competitor in the U.S. market for BIOs with a share of 63.6%.". "The binocular indirect ophthalmoscope market has seen a great deal of innovation over the years. Keeler Instruments has been at the forefront of this innovation".

Keeler Instruments, Inc. • 456 Parkway • Broomall, PA 19008 • Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

Hungry for success?

At Jobson, we have more effective ways for you to reach the optical market than anyone. So our approach to serving clients is unique. First, we develop a thorough understanding of your specific goals. This understanding, plus our extensive offering of products and services, enables us to then suggest solutions that will help achieve those goals. This often includes innovative ideas and premium positions. For advertising information contact Michele Barrett (610-492-1014, mbarrett@jobson.com) or Jim Henne (610-492-1017, jhenne@jobson.com). Let us satisfy your hunger for success.

REVIEW® of Ophthalmology | REVIEW® of Ophthalmology www.revophth.com | RETINA ONLINE

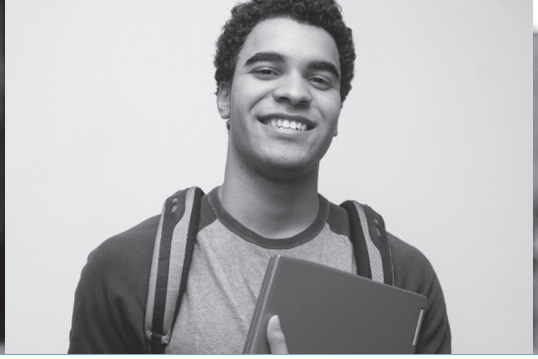
Jobson Optical Group

The vision to help you succeed

Left your *Review of Ophthalmology* magazine at the office? No problem!

Get *Review* sent to your desktop or mobile device!

Just simply go to www.revophth.com and click on the digimag link to get your current issue.

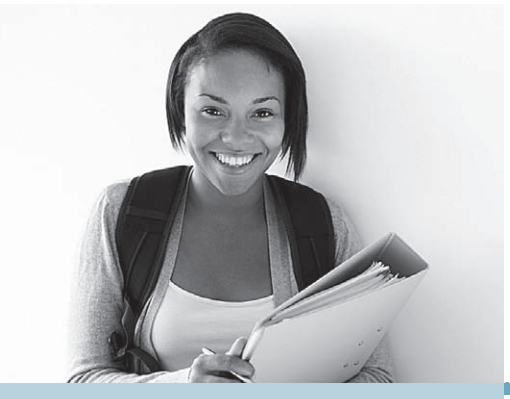




The Rick Bay Foundation

for Excellence in Eyecare Education

www.rickbayfoundation.org

Support the Education of Future Healthcare & Eyecare Professionals



About Rick

Rick Bay served as the publisher of The *Review* Group since 1991.

To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

Scholarships will be awarded to advance the education of students in both ***Optometry*** and ***Ophthalmology***, and will be chosen by their school based on qualities that embody Rick's commitment to the profession, including integrity, compassion, partnership and dedication to the greater good.

Interested in being a partner with us?

Visit www.rickbayfoundation.org

THE RICK BAY FOUNDATION
for Excellence in Eyecare Education


How to Diagnose and Manage Coats' Disease

Intravitreal therapy represents an exciting addition to traditional ablative techniques for this retinal vascular disorder.

John D. Pitcher III, MD, and Carl D. Regillo, MD, Philadelphia

Coats' disease is an idiopathic retinal vascular disorder characterized by telangiectasias and exudation.[1] The clinical features were first described in 1908 by George Coats, a Scottish ophthalmologist. He observed a variable spectrum of small aneurysms and dilated capillaries with sub- and intra-retinal fluid and exudate accumulation in young male patients. This process may progress to involve the posterior pole, causing substantial vision loss in advanced cases. Early detection and appropriate treatment are necessary to limit sight-threatening sequelae.

Pathophysiology

Mutations in NDP, a gene coding for norrin, have been implicated in diseases involving retinal vasculogenesis, including Coats' disease.[2] A "Coats'-like" retinopathy has been observed in genetic syndromes such as autosomal dominant facioscapulohumeral muscular dystrophy (Hallermann-Streiff syndrome) and familial renal-retinal dystrophy (Senior-Loken syndrome).[3,4] Despite these associations, sporadic cases are the rule, and no hereditary pattern has been consistently identified.

Histopathologic studies of Coats' specimens demonstrate pericyte loss, which allows for the formation of aneurysms. Breakdown of the endothelial blood-retinal barrier causes leakage into the vessel wall, leading to dilation and telangiectasis. This pathologic mechanism is similar to that observed in diabetic retinopathy, which has implications in treatment.[5,6]

Clinical Presentation

The majority of Coats' disease is diagnosed between ages 8 and 16.[1] There are reports of cases presenting in adulthood, but this is less common.[7,8] Greater than 75 percent of patients are male, and 95 percent of cases are unilateral.[1] Alternative diagnoses should especially be considered in female, adult-onset or bilateral cases.

There is a broad spectrum of clinical presentation in Coats' disease. Some patients may be asymptomatic and are diagnosed on routine ophthalmologic examination. Decreased vision, strabismus and leukocoria are the most common presenting features in Coats' disease.[11] Poor initial visual acuity, which is common, correlates with a poorer long-term prognosis.[9] Anterior segment findings, such as corneal edema, exudate in the aqueous humor or neovascularization of the iris, are

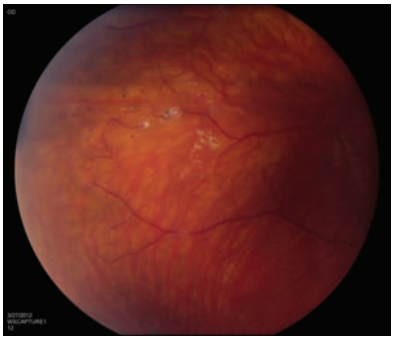
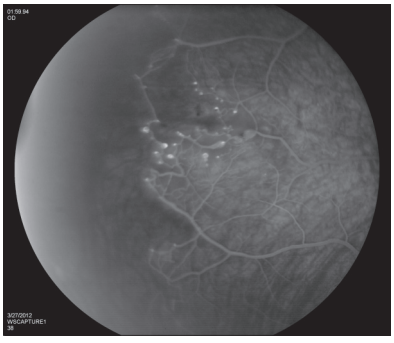



Figure 1. Retinal vessel telangiectasia and aneurysmal dilations are the hallmark of stage 1 Coats' disease.

This article has no commercial sponsorship.

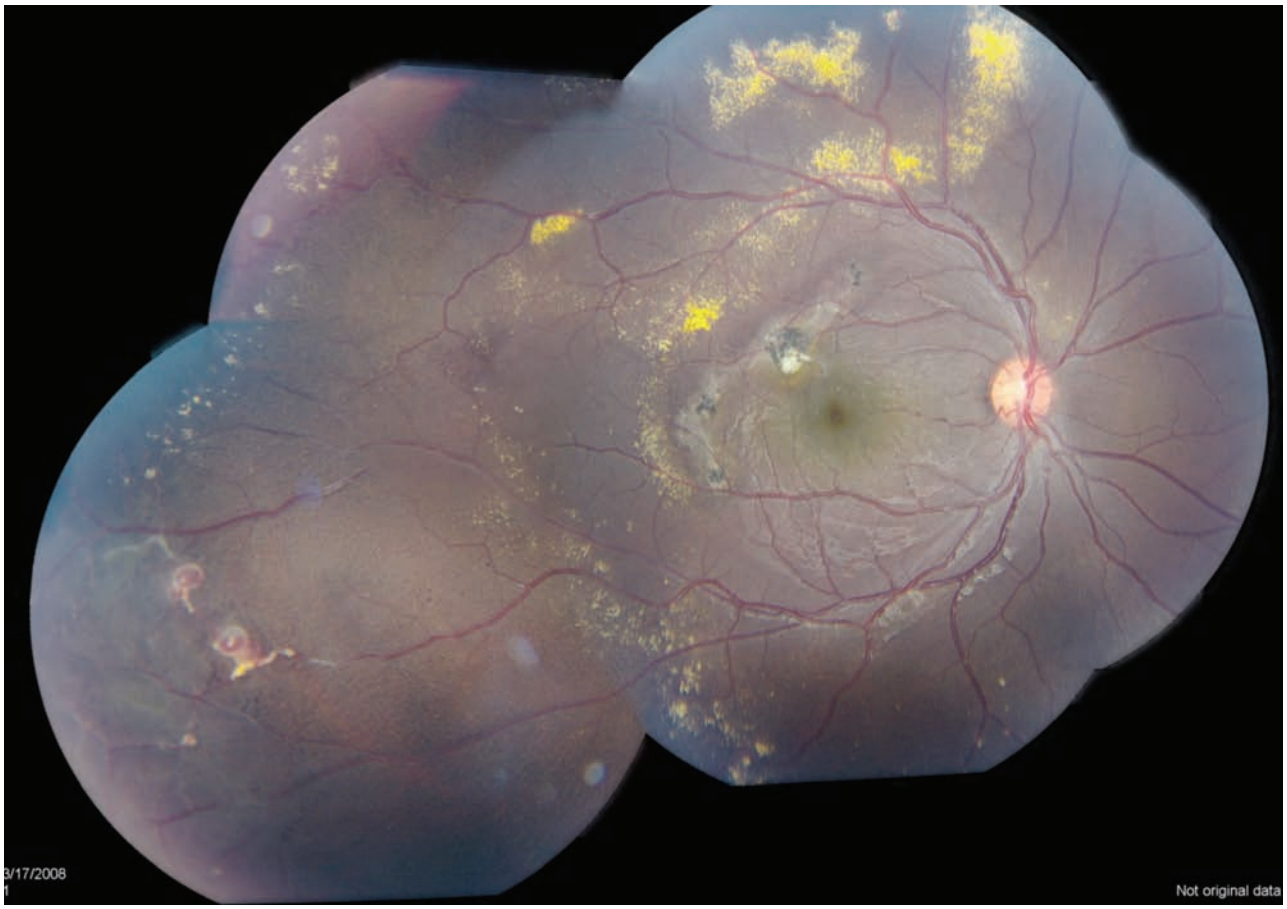


Figure 2. Fusiform arteriolar dilatation ("light bulb" aneurysms), venous sheathing and beading, and exudation in a patient with Coats' disease.

present only in advanced cases. Given the variety of clinical features, it is always important to rule out imitators, particularly retinoblastoma *(See Table 1)*.[10]

In 2000, a classification system was proposed using funduscopic features of the disease *(See Table 2)*.[11] Retinal vessel telangiectasia and aneurysmal dilations *(See Figure 1)* are the hallmark of stage 1, and are most commonly noted anterior to the equator in the temporal and inferior quadrants. Fusiform arteriolar dilatation ("light bulb" aneurysms) and venous sheathing or beading may occur *(See Figure 2)*. The presence of exudates indicates stage 2, and stage 3 includes both subtotal and total retinal detachment. Pre- and subretinal fibrosis may be present in advanced disease. Cases with secondary glaucoma and pre-phthisis bulbi are classified as stage 4 and 5, respectively. The natural history is highly variable but progression is generally expected. Staging can be helpful in monitoring disease activity and response to treatment. Late reactivation is not uncommon and lifetime surveillance is prudent.

Table 1. The Differential Diagnosis of Coats' Disease

Unilateral	Bilateral
Retinoblastoma	
Persistent fetal vasculature	Retinopathy of prematurity
Toxocariasis	Familial exudative vitreoretinopathy
Retinal capillary hemangioma	Incontinentia pigmenti

Ancillary Testing

Ophthalmoscopy is often sufficient to make the diagnosis of Coats' disease. Examination under anesthesia may be necessary in young children. Fundus photography is useful at baseline and on subsequent follow-up visits to monitor for progression and identify new areas of disease activity. Fluorescein angiography provides optimal visualization of vascular abnormalities which hyperfluoresce early and leak late *(See Figure 1)*, helping target treatment. Optical coherence tomography, including intraoperative techniques,[12] has been reported as useful in local-

izing subtle intraretinal edema or subretinal fluid, as well as monitoring response to therapy.[13,14] In advanced disease with substantial subretinal fluid, B scan ultrasound may be helpful to rule out an underlying mass lesion.[15] CT and MRI may also have some utility in atypical cases to identify calcification or enhancement that may be indicative of retinoblastoma.

Treatment

Many patients develop significant retinal detachment with exudates, which have a predilection for the macula, possibly due to currents of subretinal fluid created by activity of the pump mechanism of the retinal pigment epithelium. Such deposits have high concentrations of protein, cholesterol, hemosiderin-laden macrophages, and RPE cells with fibrous metaplasia.[16,17] This can lead to subfoveal fibrotic nodules with a particularly poor prognosis. Although observation may be appropriate in some very limited peripheral stage 1 Coats' disease, early ablative or combination therapy can limit exudation and, ultimately, prevent vision loss.

Laser photocoagulation is the modality of choice for mild to moderate disease with exudation. In the Shields' classification system proposed in 2000, stage 1 and 2, leaking telangiectases and aneurysms, can be directly treated with good results *(See Figure 3)*.[18,19] Scatter or barricade strategies are generally less efficacious. Multiple sessions are often necessary as new lesions become clinically evident.[1]

If there is significant subretinal fluid, as in stage 3 disease, cryotherapy may be required. Exudation can increase immediately after treatment, especially if a substantial area is involved.[11] Retinal contracture and folds may also occur, and it is generally recommended that only two quadrants be treated at a time, and that sessions be separated by at least one month.

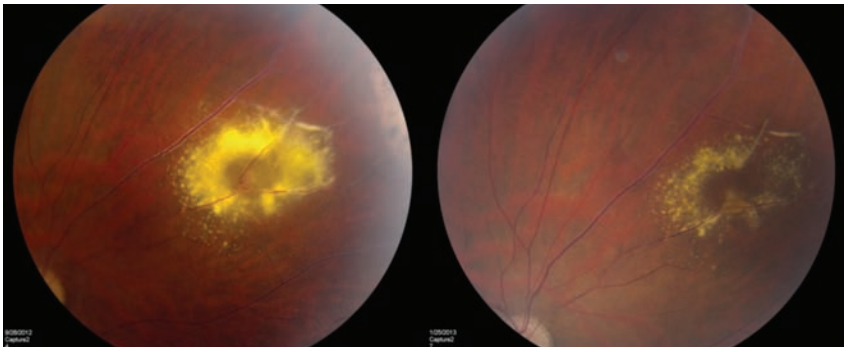


Figure 3. A 16-year-old young man with Coats' disease presented with a retinal arterial aneurysm associated with active exudation (left). Four months after a single round of focal laser ablation, the exudates have nearly resolved (right).

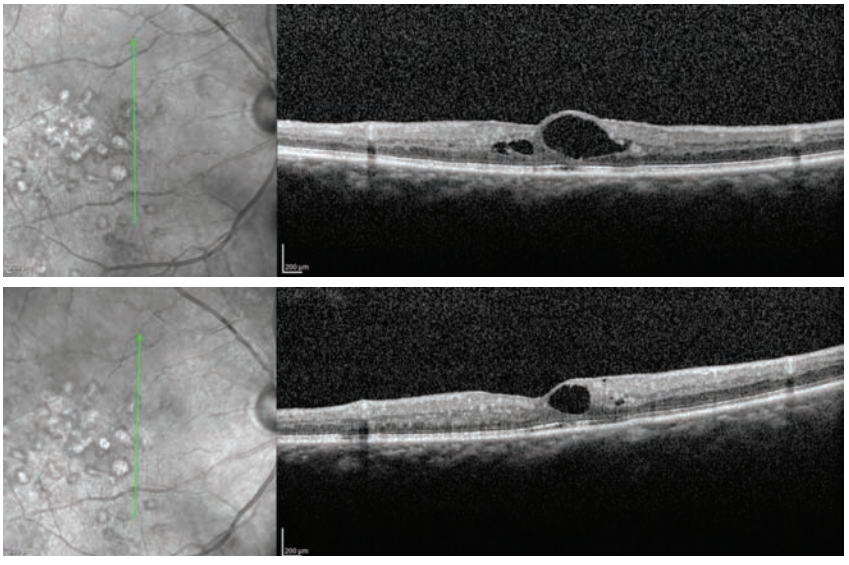


Figure 4. Optical coherence tomography before (above) and one month after (below) intravitreal bevacizumab in a patient with Coats' disease. Intraretinal fluid and cysts have diminished with treatment.

Laser photocoagulation to barricade fluid prior to cryotherapy may help limit progression of subretinal fluid.[20]

The era of intravitreal injections has yielded several new options for managing the exudative complications of Coats' disease. In the absence of prospective comparative studies, it

Table 2. Staging and Visual Acuity in Coats' Disease

Stage	Findings	Vision <20/200
1	Retinal vessel telangiectasia and aneurysms	Rare
2a 2b	Exudate, extra-foveal Exudate, foveal	50 percent
3a 3b	Subtotal exudative retinal detachment Total exudative retinal detachment	75 percent
4	Secondary glaucoma	
5	End-stage (pre-phthisis) disease	~100 percent

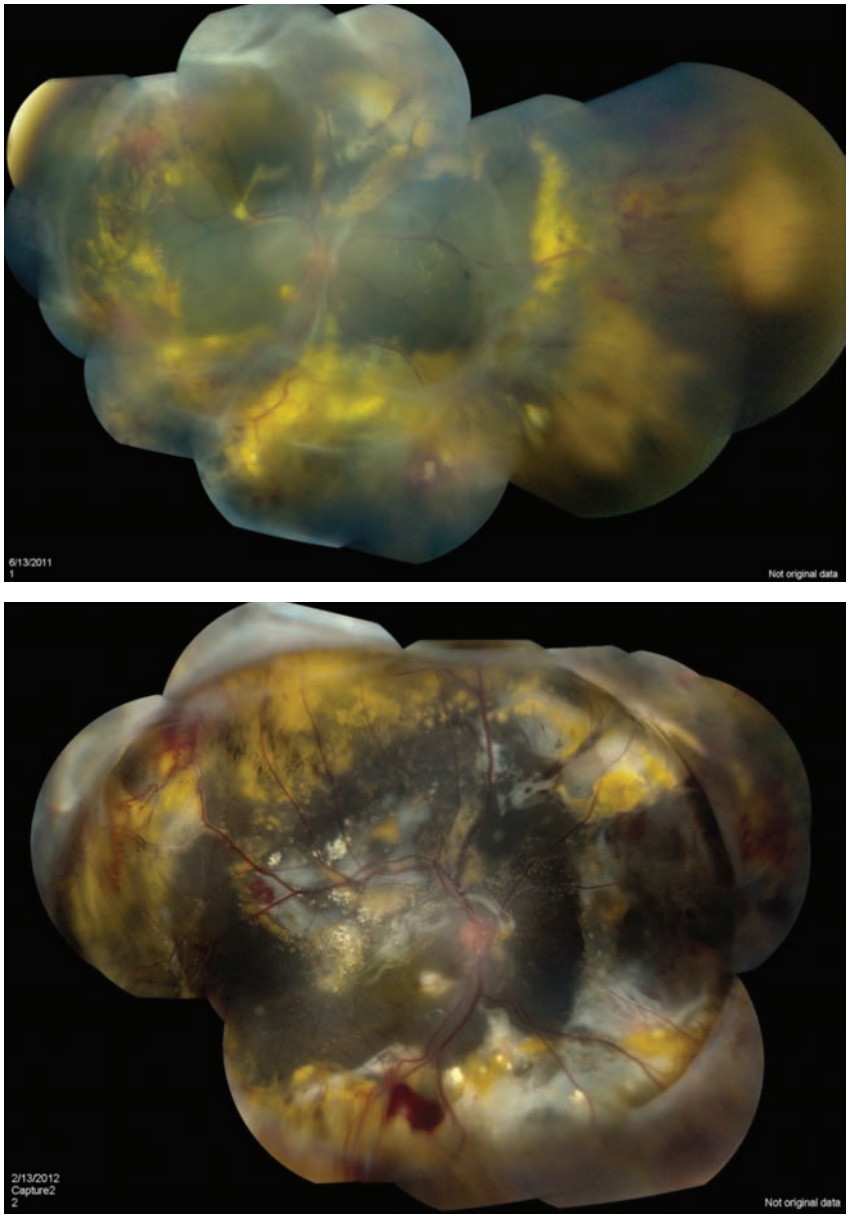


Figure 5. A middle-aged man presented with late-stage Coats' disease associated with preretinal fibrosis and vitreoretinal traction (top) requiring pars plana vitrectomy, membrane peel and silicone oil tamponade. Eight months following the procedure, the disease process had stabilized (bottom) but visual acuity remained poor.

is best to consider pharmacotherapy as an adjuvant to ablative techniques. Combination therapy (e.g., intravitreal triamcinolone or anti-vascular endothelial growth factor agents before or at the time of ablation) offers the potential benefit of immediate stabilization (or improvement) with long-term control.

Yu-Guang He, MD, and colleagues reported a mean vitreous VEGF level of 2,394.5 pg/ml in Coats' patients compared with 15.3 pg/ml in controls.[21] Although the exact pathophysiologic mechanism needs further study, there seem to be therapeutic implications. In the past six years, 19 authors have published cases or series of anti-VEGF therapy for Coats' disease in stages 2 to 4. Nearly all have shown positive results with respect to visual or anatomic outcomes *(See Figure 4)*. In a recent retrospective review with age-matched controls, intravitreal bevacizumab plus thermal ablation was shown to have fewer treatment failures over laser alone.[22] Although most reports are overwhelmingly favorable, some have cautioned of increased vitreoretinal traction following intravitreal anti-VEGF therapy in stages 2 to 3 Coats' disease.[23]

Intravitreal triamcinolone may be especially beneficial in eyes with total bullous exudative detachment (TBERD, stage 3b).[24] Total resolution of subretinal fluid has been reported with a single injection.[25] The risks and benefits should be carefully considered since cataract, elevations in intraocular pressure and other injection-related complications are all possibilities. We generally prefer administration of 2 mg preparations of IVT over 4 mg, as the former is associated with a lower rate of elevated IOP.

Surgical intervention is rarely necessary and is reserved for late stage or refractory disease. In select cases, patients with extensive retinal detachment may benefit from vitrectomy. In particular, patients with pre-retinal membranes or contribution from tractional components may require membrane peel *(See Figure 5)*. Enucleation may be necessary in stage 4 and 5 disease, where a blind, painful eye may develop.

More than a century has passed since the original description of Coats' disease. Our understanding of the underlying pathophysiology continues to improve, as do our diagnostic and treatment modalities. Intravitreal therapy represents an exciting addition to traditional ablative techniques. Early identification of exudation and appropriately aggressive intervention can modify the course of the disease and improve

patient outcomes. REVIEW

Dr. Pitcher is XXXXX axxxx xxxxx at xxxxxx at the aXXXXXXX *Dr. Regillo is director of the Retina Service of Wills Eye Institute, and a professor of ophthalmology at Thomas Jefferson University School of Medicine.*

1. Shields JA, Shields CL, Honavar SG, Demirci H. Clinical variations and complications of Coats' disease in 150 cases: The 2000 Sanford Gifford Memorial Lecture. Am J Ophthalmol 2001;131:561-571.
2. Black GC, Perveen R, Bonshek R, Cahill M, Clayton-Smith J, et al. Coats' disease of the retina (unilateral retinal telangiectasis) caused by somatic mutation in the NDP gene: A role for norrin in retinal angiogenesis. Hum Mol Genet 1999;8(11):2031-2035.
3. Newell SW, Hall BD, Anderson CW, Lim ES. Hallermann-Streiff syndrome with Coats' disease. J Pediatr Ophthalmol Strabismus 1994;31:123-125.
4. Schuman JS, Lieberman KV, Friedman AH, Berger M, Schoeneman MJ. Senior-Loken syndrome (familial renal-retinal dystrophy) and Coats' disease. Am J Ophthalmol 1985;100:822-827.
5. Egbert PR, Chan CC, Winter FC. Flat preparations of the retinal vessels in Coats' disease. J Pediatr Ophthalmol 1976;13:336-339.
6. Fernandes BF, Odashiro AN, Maloney S, Sajdenweber ME, et al. Clinical-histopathological correlation in a case of Coats' disease. Diagn Pathol 2006;1:24.
7. Smithen LM, Brown GC, Brucker AJ, Yannuzzi LA, et al. Coats' disease diagnosed in adulthood. Ophthalmology 2005;112:1072-1078.
8. Shienbaum G, Tasman WS: Coats' disease. A lifetime disease. Retina 2006;26:422-424.
9. Budning AS, Heon E, Gallie BL. Visual prognosis of Coats' disease. J AAPOS 1998;2(6):356-359.
10. Shields CL, Uysal Y, Benevides R, Eagle RC Jr, et al. Retinoblastoma in an eye with features of Coats' disease. J Pediatr Ophthalmol Strabismus 2006;43:313-315.
11. Shields JA, Shields CL, Honavar SG, Demirci H, Cater J. Classification and management of Coats disease: The 2000 Proctor Lecture. Am J Ophthalmol 2001;131:572-583.
12. Henry CR, Berrocal AM, Hess DJ, Murray TG. Intraoperative spectral-domain optical coherence tomography in Coats' disease. Opthalmic Surg Lasers Imaging 2012 Jul 26;43:e80-84.
13. Kessner R, Barak A, Neudorfer M. Intraretinal exudates in Coats' disease as demonstrated by spectral-domain OCT. Case Rep Ophthalmol 2012;3(1):11-15.
14. Jun JH, Kim YC, Kim KS. Resolution of severe macular edema in adult Coats' disease with intravitreal triamcinolone and bevacizumab injection. Korean J Ophthalmol 2008;22(3):190-193.
15. Atta HR, Watson NJ. Echographic diagnosis in advanced Coats' disease. Eye 1992;6:80-85.
16. Hsu J, Forbes B, Maguire AM. Total exudative retinal detachment in Coats' disease. Biochemical analysis of the subretinal exudate. Retina 2006;26:831-833.
17. Khurana RN, Samuel MA, Murphree AL, Loo RH, et al. Subfoveal nodule in Coats' disease. Clin Exp Ophthalmol 2006;33(3):301-302.
18. Couvillion SS, Margolis R, Mavrofjides E, Hess D, Murray TG. Laser treatment of Coats' disease. J Pediatr Ophthalmol Strabismus 2005;42:367-368.
19. Scheffler AC, Berrocal AM, Murray TG. Advanced Coats' disease. Management with repetitive aggressive laser ablation therapy. Retina 2008;28:38-41.
20. Budning AS, Heon E, Gallie BL. Visual prognosis of Coats' disease. J AAPOS 1998;2(6):356-359.
21. He YG, Wang H, Zhao B, Lee J, Bahl D, McCluskey J. Elevated vascular endothelial growth factor level in Coats' disease and possible therapeutic role of bevacizumab. Graefe's Arch Clin Exp Ophthalmol 2010;248(10):1519-21.
22. Ray R, Baranano DE, Hubbard GB. Treatment of Coats' disease with intravitreal bevacizumab. Br J Ophthalmol 2013;97(3)272-277.
23. Ramasubramanian A, Shields CL. Bevacizumab for Coats' disease with exudative retinal detachment and risk of vitreoretinal traction. Br J Ophthalmol 2011;96(3):356-359.
24. Othman IS, Moussa M, Bouhaimed M. Management of lipid exudates in Coats disease by adjuvant intravitreal triamcinolone: Effects and complications. Br J Ophthalmol 2010;94:606-610.
25. Ghazi NG, Al Shamsi H, Larsson J, Abboud E. Intravitreal triamcinolone in Coats' disease. Ophthalmology 2012;119(3):648-649.

A Street-Level Look At Urban Allergy

How living in an urban environment may foster an allergic response and the potential treatments waiting in the wings.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and Daniel A. Gamache, PhD, Andover, Mass.

Allergy has been called "the 21st century disease."[1] The increasing prevalence of allergy has been linked to global industrialization and urbanization, with prevalence rising at the highest rates in nations where development is greatest, particularly in Asia.[1] Urbanization has so impacted the environment that our adaptive immune system has responded with increasingly complex and severe reactions. The exposed mucosa of the eye represents a dynamic immunological system that is particularly sensitive to this changing landscape. Under these conditions, the mechanisms in place to protect the ocular surface and respond to pollutant-reinforced allergen attacks are being tested as never before.

The physiological systems that evolved to protect the ocular surface include the blink and tear reflexes, and the host of humoral factors that control the level and nature of immune responses. For patients who develop ocular allergy, antihistamines and steroids have demonstrated therapeutic value beyond the natural defenses, but there is a growing subpopulation of allergic conjunctivitis patients who respond poorly to available treatments. These patients suffer from a persistent conjunctivitis and a chronic allergic inflammation. In this month's column, we'll discuss the environmental and cultural factors that promote urban allergy, as well as the key mediators of the allergic inflammatory response that may provide potential therapeutic targets for new treatments.

Urban Enhancements to Allergy

Growing urbanization around the globe has led to climate change and increased local levels of airborne pollutants, primarily due to vehicle exhaust. These environmental changes have profoundly influenced adaptive immune responses in exposed individuals.[2,3] Increased global temperatures have expanded the geographic migration of vegetation and have led to an accelerated onset and extended duration of the growing season. Also, urban areas are typically characterized by more plant homogeneity than rural areas, which promotes greater pollination rates and higher pollen levels per plant.[4] These factors combine to significantly increase the antigen burden on urbanites with seasonal allergies.

Longer and more intense pollen seasons, combined with urban area pollutants, create a perfect storm for exposed mucosal tissues. The major urban pollutants include ozone, nitrogen dioxide and particulate matter. These pollutants have the capacity to interact with and structurally modify airborne pollens, thereby enhancing their antigenicity. However, of even greater interest, urban-area pollutants can function as immune system adjuvants. For example, ozone subjects the mucosal epithelium to oxidative stress and promotes a pro-inflammatory response. This is associated with epithelial barrier disruption and the local production of inflammatory cytokines.[2,5] Inflammatory disruption of mucosal barrier integrity then facilitates tissue penetration by allergen and interaction with cells of the immune system. In this way, urban pollutants have the capacity to prime or sensitize the immune system for an allergic response.

However, things get even worse for the city dweller. Not only are airborne pollutants and pollens modifying immune responses, but the comparative lack of an abundant and diverse micro-

This article has no commercial sponsorship.

bial environment that exists in rural and underdeveloped areas, incongruously may threaten immune health. The hygiene hypothesis of atopic diseases proposes that lack of early life exposure to pathogens diverts T cells from their original *raison d'etre* of microbial defense in favor of atopy, and the recognition of harmless proteins as antigenic. Our stressful and unhealthy lifestyle is another component of urban/Western culture that predisposes toward allergy, particularly the Western diet. A recent U.S. survey found that obesity and associated systemic inflammation are risk factors for allergy in children and adolescents.[6] The concept that systemic inflammation is associated with mucosal allergy may be related to complex immune pathways involving priming and tolerance (elucidated in November 2012's Therapeutic Topics). Together, these factors point to the importance of general health issues as additional risk factors for atopic disease.

Emerging Drug Candidates for Chronic Allergy

Immune Response	Target	Drug	Chemical Class	Sponsor
Mast cell activation	Syk Syk/JAK	R343 PRT2070, PRT 2607	new chemical entity (small molecule)	Rigel Portola/Aciex
Immune cell receptor activation	CRTh2 H4	QAW039 UR-63325	NCE NCE	Novartis Palau
Th2 cytokine activity	IL-4/IL-13 JAK IL-5	pitrakinra dupilumab R256 mepolizumab benralizumab	monoclonal antibody Mab NCE Mab Mab	Aerovant Sanofi/Regeneron Rigel GSK AstraZeneca
Tissue-derived Th2 drivers	TSLP Eotaxin	AMG157 MEDI-9929 bertilimumab	Mab Mab Mab	Amgen AstraZeneca Ico Therapeutics
Innate response	TLR	AZD8848	single-stranded RNA	AstraZeneca

Patients with symptomology consistent with "urban allergy" exhibit signs and symptoms of disease which, when compared with others with allergies, are generally more chronic, more severe and more resistant to currently employed therapies. Although precise numbers are not available, these patients may represent up to 30 to 40 percent of the allergic conjunctivitis population. This subset also includes patients who are poly-sensitive, meaning they are allergic to more than one type of allergen (pollens as well as dust mites, for example). The increase in patients with multiple allergies may be part of the explanation for the growing chronic population. In addition, patients with vernal and atopic keratoconjunctivitis have chronic and severe disease that can be sight-threatening and poorly responsive to currently approved drugs. Taken together, in this substantial population of chronic ocular allergy patients, inflammation drives the intensity of the response and represents a significant unmet medical need.

Recruits for Urban Warfare

Allergic inflammation occurs in sensitized tissues where a predominately Th2-lymphocyte immune response has established high local levels of antigen specific-IgE bound mast cells. Antigen challenge triggers release of chemotactic signaling molecules that drive the accumulation of leukocytes including neutrophils, basophils, eosinophils and lymphocytes into the sensitized tissue. The goal of most emerging therapies is to disrupt this recruitment, prevent the buildup of inflammatory cells, and allow the natural cycle of inflammation to proceed to resolution.

In sensitized individuals, antigen is captured by specific IgE bound to the high affinity receptor FcεRI on the surface of mast cells, an event that triggers degranulation and activation. Critical to this mast-cell response to antigen is activation of spleen tyrosine kinase. Mast cells deficient in Syk do not degranulate or synthesize inflammatory mediators upon antigen-induced aggregation of FcεRI.[7] Syk-induced activation of phospholipase C generates second messengers that increase intracellular calcium, which is required for mast-cell degranulation and histamine release. In addition, phospholipase A2 is activated to liberate membrane-bound arachidonic acid for conversion into prostaglandins and leukotrienes.

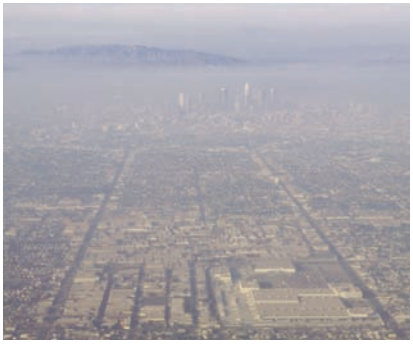
Syk-induced transcription factor activation leads to transcription and translation of genes encoding several pro-inflammatory cytokines and chemokines.[8] These essential roles played by Syk in the production of a host of pro-inflammatory mediators provide the rationale for its development as a therapeutic target for the treatment of allergic conjunctivitis and associated

allergic inflammation. The potent Syk inhibitor R343 (Rigel Pharmaceuticals) is currently in development for the treatment of patients with allergic asthma.

While mast cells are primarily thought of as suppliers of the histamine that elicits the classic signs and symptoms of allergic conjunctivitis, they are also a source of cytokines and chemotactic factors that are key to subsequent recruitment of inflammatory cells. One such chemo-attractant is histamine itself, which exerts an attractant effect via histamine H4 receptors expressed on eosinophils, T-lymphocytes and other mast cells.[9] Alcaftadine (Allergan), a dual antihistamine/mast-cell stabilizer, is known to also have H4R-antagonistic properties that may contribute to its anti-inflammatory effects. Part of this effect may also be based upon an ability to stabilize epithelial tight junctions and maintain the barrier function of the epithelium.[10] Selective H4R antagonists including UR-63325 (Palau Pharma S.A.) have entered clinical trials for the treatment of allergic respiratory diseases, including asthma.

Like histamine, PGD2 is involved in both the early and late phases of allergy. Mast-cell derived PGD2 activates receptors on Th2 cells to promote eosinophil chemotaxis and cytokine production. Antagonists of the PGD2 receptors have been effective in animal models of ocular allergy[11] and several compounds in this class, including QAW039 (Novartis), are now in clinical trials for the treatment of asthma.

Eosinophils are the hallmark cell type of allergic inflammation, and are of particular concern due to the tissue-destructive properties of their cationic granule proteins. Major basic protein is the most abundant eosinophil-derived granule protein, and it is a potent disruptor of cell membranes. Eosinophil peroxidase enzymatically generates oxidants that are also cytotoxic. In the eye, eosinophilic mediators contribute significantly to the breakdown of protective barriers, promoting tissue remodeling and further lymphocyte accumulation.



Urban allergens in action: The American Lung Association says the Los Angeles/Long Beach/Riverside area has the fourth-worst air quality in the United States.[20]

Eotaxin is a potent chemotactic factor for eosinophils that is produced by fibroblasts, epithelial cells, endothelial cells, T-lymphocytes and eosinophils. Exposure of corneal fibroblasts to the Th2 cytokines, IL-4 and IL-13, is a major stimulus for local production of eotaxin. TNFα also induces eotaxin release and synergizes with IL-4 and IL-13.[12] Recently, several compounds have been developed that interfere with eotaxin signaling by blocking activation of the eotaxin receptor (also referred to as CCR3). ICo Therapeutics recently announced plans to initiate a clinical trial of bertilimumab, a human anti-eotaxin-1 monoclonal antibody, for treatment of vernal keratoconjunctivitis.

The Th2 cytokines IL-4 and IL-13 are the major agents of inflammation in the urban allergy battle; this makes the IL-4 receptor a key potential target since it acts as receptor for both cytokines. Pitrakinra (Aerovant) is a recombinant human form of IL-4 that functions as an IL-4R antagonist that's demonstrated efficacy in asthma clinical trials.[13] Another IL-4R antagonist now in clinical trials as an anti-allergic is dupilumab (Sanofi/Regeneron). The JAK kinase inhibitor R256 (Rigel Pharma), which also acts to suppress IL-4 and IL-13 signaling, is entering clinical trials as well.

Another key Th2 cytokine, IL-5, mediates the differentiation, proliferation, activation, and chemotaxis of eosinophils and synergizes with IL-4, IL-13 and eotaxin to promote allergic inflammation.[14] Anti IL-5 (mepolizumab; GSK) and anti-IL-5R (benralizumab; AstraZeneca) are in clinical development for allergic asthma.

A link between innate and adaptive immunity has been the subject of much recent immunology research. Resident tissue cells respond to immune cell mediators by producing factors that further modulate immune responsiveness. Epithelial-cell derived cytokines such as IL-25, IL-33 and thymic stromal lympho-protein play key roles in chronic allergic inflammatory responses. TSLP promotes Th2 differentiation and proliferation, directly enhances effector functions of Th2 cells and activates mast cells and eosinophils.[15]

It has been reported in animal studies that short ragweed pollen stimulates epithelial TSLP production and triggers Th2 allergic inflammation by activating Toll-like receptor 4.[16] Toll receptors are widely expressed pattern recognition receptors that bind molecular sequences conserved by a variety of pathogens, including bacteria and viruses. Activation of TLRs leads to production of cytokines and chemokines that stimulate an immune response. In addition, activation of TLRs can synergize with FcεRI signaling, potentially enhancing the response of mast cells to antigen.[17] Antibodies that target TSLP (AMG157, Amgen; MEDI-9929, AstraZeneca) and a TLR modulator (AZD8848, AstraZeneca) are in early development for the treatment of asthma, and may be future therapies for severe or chronic allergic conjunctivitis.

Outlook for the Urbanite

The variety of emerging therapies for allergic inflammation reflects the complexity of the pathophysiology of these conditions. Currently available immune-modulators may provide an option but these drugs inhibit all T-lymphocytes, including suppressor T-regulatory cells. More selective targeting could improve the therapeutic index of drugs to help fill this unmet medical need.

There is a clear rationale for evaluating therapies originally developed for respiratory allergy as treatments for ocular allergic inflammation. For example, the anti-IgE drug omalizumab (Xolair, Novartis), approved by the Food and Drug Administration for the treatment of allergic asthma and rhinitis, has been shown to be effective in reducing ocular symptoms in severe allergic conjunctivitis.[18] The same may be true for marketed anti-TNF and PDE4 inhibitor compounds that have demonstrated efficacy in respiratory inflammatory diseases. In addition, local administration of anti-allergy drugs provides ocular efficacy and pharmacokinetic advantages over systemically delivered treatments.[19]

The picture of ocular allergic disease we're left with is one that is more akin to a Los Angeles freeway interchange than a rural crossroad. As our understanding of the immune system's complex networks of signaling checks and balances expands, we recognize that changes in the nature and prevalence of ocular allergy are, in large part, a result of an immunological response to a moving target. It's vital to remember that the best way to treat allergy is to remove the irritant, whether it's pollen or pollution. In addition, our goal should also be to identify one or more new therapeutic approaches to the problem of chronic, urban allergy from either new or repurposed biologicals or small molecules; combining these with new drug delivery paradigms will be key to fighting urban allergy in the 21st century. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. Gamache is Director-Ophthalmic Pharmaceuticals Market Research at Market Scope, LLC.

1. Pawankar R, Baena-Cagnani CE, et al. State of World Allergy Report 2008. WAO Journal 2008;S4-S17.
2. D'Amato G. Effects of climatic changes and urban air pollution on the rising trends of respiratory allergy and asthma. Multidiscip Respir Med. 2011;6:1:28-37.
3. D'Amato G, Rottem M, et al. Climate change, migration and allergic respiratory diseases: An update for the allergist. WAO Journal 2011;4:121-125.
4. Knapp S, Kühn I, et al. Challenging urban species diversity: Contrasting phylogenetic patterns across plant functional groups in Germany. Eco Lets [abstract]. 2008 [cited 2010 Jun 27];11:10:1054. Available from: Wiley InterScience. http://interscience.wiley.com.
5. Bayram H, Sapsford RJ, et al. Effect of ozone and nitrogen dioxide on the release of proinflammatory mediators from bronchial epithelial cells of nonatopic nonasthmatic subjects and atopic asthmatic patients in vitro. J Allergy Clinical Immunol 2001;107:287-294.
6. Visness CM, London SJ, et al. Association of obesity with IgE and allergy symptoms in children and adolescents: Results from NHANES 2005-2006. J Allergy Clinical Immunol 2009;123:5:1163-1169.
7. Costello PS, Turner M, et al. Critical role for the tyrosine kinase Syk in signaling through the high affinity IgE receptor of mast cells. Oncogene 1996;13:12:2595-2605.
8. Sirganian RP, deCastro Ro, et al. Mast cell signaling: The role of protein tyrosine kinase Syk, its activation and screening methods for new pathway participants. FEBS Letters 2010;584:24:4933-4940.
9. Zampeli E, Tiligada E. The role of histamine H4 receptor in immune and inflammatory disorders. British Journal of Pharmacology 2009;157:24-33.
10. Ono SJ, Lane KJ. Comparison of effects of alcaftadine and olopatadine on conjunctival epithelium and eosinophil recruitment in a murine model of allergic conjunctivitis. Drug Design, Development and Therapy 2011;5:1–8.
11. Stebbins KJ, Broadhead AR, et al. DP2 (CRTh2) Antagonism Reduces Ocular Inflammation Induced by Allergen Challenge and Respiratory Syncytial Virus. Int Arch Allergy Immunol 2012;157:259–268.
12. Fukuda K, Kumagai N. Fibroblasts as local immune modulators in ocular allergic disease. Allergol Int. 2006;55:2:121-129.
13. Wenzel S, Wilbraham D, et al. Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. Lancet 2007;370:1422–1431.
14. Rosenberg HF, Phipps S, et al. Eosinophil trafficking in allergy and asthma. J Allergy Clin Immunol 2007;119:1303–1310.
15. Ziegler SF, Artis D. Sensing the outside world: TSLP regulates barrier immunity. Nature Immunology 2010;11:289-293.
16. Li D, Zhang L, et al. Short ragweed pollen triggers allergic inflammation through Toll-like receptor 4-dependent thymic stromal lymphoprotein/OX40 ligand/OX40 signaling pathways. J Allergy Clin Immunol 2011;128:6:1318-1325.
17. Sandig H, Bulfone-Paus S. TLR signaling in mast cells: Common and unique features. Frontiers Immunology 2012;3:185-193.
18. Williams PB, Simon DJ, et al. Omalizumab improves symptoms of severe ocular allergy. Invest Ophthalmol Vis Sci 2005;46:942.
19. Abelson MB, Lanier RQ. The added benefit of local Patanol therapy when combined with systemic Claritin for the inhibition of ocular itching in the conjunctival antigen challenge model. Acta Ophthalmol Scand Suppl 1999;228:53-56.
20. http://www.stateoftheair.org/2013/city-rankings/most-polluted-cities.html. accessed July 7, 2013.


SLT Today: An Effective Alternative to Drops

Laser trabeculoplasty continues to gain favor as a reliable means to reduce intraocular pressure.

L. Jay Katz MD, Philadelphia

In the past few decades ophthalmologists have been gradually using laser trabeculoplasty earlier and earlier in their glaucoma treatment protocols. When I first started my training, it was common practice to use every medication possible—sometimes even oral medications like acetazolamide—before resorting to laser trabeculoplasty. Now it's pretty rare to see an ophthalmologist prescribe more than two or three topical medications before selective laser trabeculoplasty comes up for discussion, and some doctors consider it after a single medication has proven insufficient.

Recent data continues to support the idea that SLT is a reasonably safe and effective first-line treatment option in open-angle glaucoma and high-risk ocular hypertension. The SLT vs. medication study,[1] a prospective, randomized clinical trial for which our clinic was the coordinating center, offered laser as a first-line option and compared outcomes with patients receiving one-drop therapy with a prostaglandin. Twenty-nine patients received SLT; 25 received medical therapy in both eyes. After nine to 12 months follow-up, intraocular pressure had fallen from 24.5 mmHg to 18.2 mmHg in the SLT group and from 24.7 mmHg to 17.7 mmHg in the medication group (not a statistically significant difference). Also, by final follow-up, 11 percent of SLT eyes had received additional SLT, while 27 percent of eyes in the medication group required additional medications.

Given its increasing popularity, I'd like to discuss some of the latest developments relating to SLT and share some thoughts regarding issues that are frequently raised during discussions about the laser.

Getting Closer to an Explanation

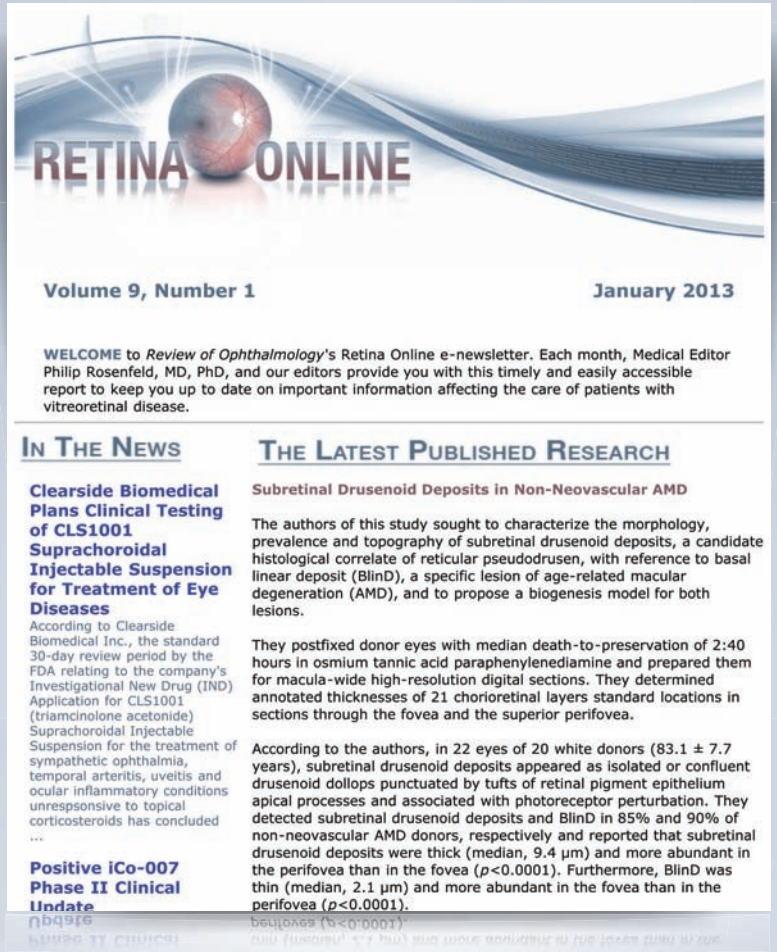
One SLT-related development of note in recent years has been progress in our understanding of how laser trabeculoplasty acts to reduce IOP. Jorge Alvarado, MD, in San Francisco, deserves a lot of credit for the work he's done investigating the way lasers affect the tissues in the angle. He's demonstrated that a whole cascade of events takes place; the laser triggers biochemical changes that lead to the production of cytokines, and macrophages are recruited to the lasered area. Among other things, this causes the intercellular junctions to loosen, allowing aqueous to get to Schlemm's canal more easily. Mark Latina, MD, the inventor of the laser, calls this a "rejuvenation" of the angle.

There's still a controversy regarding whether SLT and prostaglandins share a common pathway for lowering pressure. Some people believe they do, saying that if you've done laser effectively and completely, prostaglandins shouldn't have any additional pressure-lowering effect. Others argue that there is still some additive effect between the two options.

So far, this hasn't been conclusively resolved. However, my experience suggests that there is, in fact, an additive effect. If I have a patient on a prostaglandin and he's not adequately controlled, I've seen an additional benefit from doing laser trabeculoplasty. The gain is not as profound as if the patient were on a beta blocker rather than a prostaglandin analog, but there is often a gain. Some would argue that this occurred because the patient wasn't being compliant with the prostaglandin, or the

This article has no commercial sponsorship.

RETINA ONLINE
E-NEWSLETTER



RETINA ONLINE

Volume 9, Number 1 January 2013

WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

IN THE NEWS

Clearside Biomedical Plans Clinical Testing of CLS1001 Suprachoroidal Injectable Suspension for Treatment of Eye Diseases

According to Clearside Biomedical Inc., the standard 30-day review period by the FDA relating to the company's Investigational New Drug (IND) Application for CLS1001 (triamcinolone acetonide) Suprachoroidal Injectable Suspension for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unrespsonsive to topical corticosteroids has concluded ...

Positive iCo-007 Phase II Clinical Update

THE LATEST PUBLISHED RESEARCH

Subretinal Drusenoid Deposits in Non-Neovascular AMD

The authors of this study sought to characterize the morphology, prevalence and topography of subretinal drusenoid deposits, a candidate histological correlate of reticular pseudodrusen, with reference to basal linear deposit (BlinD), a specific lesion of age-related macular degeneration (AMD), and to propose a biogenesis model for both lesions.

They postfixed donor eyes with median death-to-preservation of 2:40 hours in osmium tannic acid paraphenylenediamine and prepared them for macula-wide high-resolution digital sections. They determined annotated thicknesses of 21 chorioretinal layers standard locations in sections through the fovea and the superior perifovea.

According to the authors, in 22 eyes of 20 white donors (83.1 ± 7.7 years), subretinal drusenoid deposits appeared as isolated or confluent drusenoid dollops punctuated by tufts of retinal pigment epithelium apical processes and associated with photoreceptor perturbation. They detected subretinal drusenoid deposits and BlinD in 85% and 90% of non-neovascular AMD donors, respectively and reported that subretinal drusenoid deposits were thick (median, 9.4 µm) and more abundant in the perifovea than in the fovea ($p<0.0001$). Furthermore, BlinD was thin (median, 2.1 µm) and more abundant in the fovea than in the perifovea ($p<0.0001$).

Once a month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with timely information and easily accessible reports that keep you up to date on important information affecting the care of patients with vitreoretinal disease.

3 EASY WAYS TO SUBSCRIBE!

http://www.jobson.com/globalemail/

Fax: 610.492.1039 or Call: 610.492.1027

REVIEW® of Ophthalmology

SLT vs. Meds Study[1]: Mean IOP at Baseline and Follow-up Visits

	Baseline	Follow-up, 4 to 6 Months	Follow-up, 9 to 12 months
Medicine group:			
Left eye	24.9 ±3.5 (30)	18.2 ±3.1 (30)	17.9 ±2.8 (24)
Right eye	24.1 ±2.6 (30)	17.6 ±3.6	17.5 ±2.8 (24)
Mean, both eyes (4 to 6 month group)	24.5 ±2.2	17.8 ±3.0 (31)	—
Mean, both eyes (9 to 12 month group)	24.7 ±2.4	—	17.7 ±2.5
SLT group:			
Left eye	25.2 ±3.2 (31)	19.1 ±3.2 (31)	18.6 ±3.2 (24)
Right eye	24.9 ±2.8 (36)	18.9 ±3.2 (36)	18.3 ±3.3 (28)
Mean, both eyes (4 to 6 month group)	25.0 ±2.2	18.9 ±2.9 (38)	—
Mean, both eyes (9 to 12 month group)	24.5 ±2.1	—	18.2 ±2.8

Numbers in parentheses = eyes in sample

SLT treatment wasn't complete. But in my experience, the additivity can't solely be explained by those caveats.

One factor that adds confusion to this is that we often talk about laser trabeculoplasty improving trabecular outflow, which is the way we think lasers work. Today there's some evidence that prostaglandins do have an effect on trabecular outflow. However, prostaglandins were originally believed to be improving uveoscleral outflow. If that's true, then it makes sense that LT and prostaglandins would be additive.

Practical Concerns

In terms of using laser trabeculoplasty in the clinic, several issues occasionally arise:

• ***When is SLT contraindicated?*** In certain situations, SLT is unlikely to be effective. If the patient has a secondary glaucoma such as neovascular glaucoma, traumatic angle recession or inflammatory glaucoma, SLT probably won't work well. Also, if a patient has severe damage and a very high pressure such as 50 mmHg and you want to get the pressure down quickly, laser may not be the best choice; in that case, medications and/or surgery would be indicated. And, of course, SLT is contraindicated if you can't see the angle structures due to factors such as corneal haze.

On the other hand, SLT can be effective when you're dealing with primary open-angle glaucoma, pseudoexfoliation glaucoma or pigmentary glaucoma.

• ***Are SLT and corticosteroids compatible?*** When considering whether it's advisable to treat a patient with both SLT and steroids, there are two possible scenarios to consider. The first is when steroid use has resulted in open-angle glaucoma: Is it advisable to treat that type of glaucoma with SLT? These patients may have been placed on topical steroids or intraocular steroids to address macular edema, or placed on oral steroids for some type of systemic or skin condition. According to a couple of small studies, laser trabeculoplasty does work pretty well at lowering pressure in these individuals.

The second scenario to consider is whether it makes sense to use anti-inflammatory drops such as steroids for a period of a few days or a week following laser treatment. This type of protocol was traditional after argon laser trabeculoplasty, which we started doing in the 1980s. We know that lasers cause a little bit of inflammation, so steroids were routinely used to suppress inflammation for about a week after the treatment.

Today, researchers like Jorge Alvarado, MD, have suggested that the inflammation produced by SLT is pretty mild and self-limiting. More important, the small amount of inflammation caused by the laser may play an important part in setting in motion the cellular biochemical processes in the angle that improve aqueous outflow, allowing the pressure to drop. For this reason, many ophthalmologists have stopped using steroids after SLT; they either use no drops postlaser or may use a topical nonsteroidal for a few days.

• ***Can SLT be combined with cataract surgery?*** Using SLT in conjunction with cataract surgery is a less-exciting alternative for lowering pressure these days, in part because we now know that the cataract surgery itself will lower the pressure in certain patients, and in part because of the minimally invasive glaucoma surgery options, or MIGS, that are now available. However, SLT may be effectively used after cataract surgery—almost as well as if the patient was still phakic. (That wasn't the case in the old days when cataract surgery required making a large incision.) So if you perform cataract surgery and the pressure doesn't come down quite as much as you'd hoped, SLT is a reasonable next step.

The Patient Attitude Factor

Patient attitudes toward firing a laser into the eye are a significant factor in how often laser trabeculoplasty is chosen. Depending on the patient's level of understanding, the reaction may be positive or negative. Individuals who are well-informed about SLT—often because they've

investigated the procedure on their own—are usually excited about doing the laser. They know it's relatively safe and painless, and they're usually aware of the side-effect issues and daily regimen associated with medications.

On the other hand, many individuals only know that lasers used in other ways are sometimes associated with pain or poor outcomes. A patient, for example, may equate SLT with the panretinal laser photocoagulation his cousin Harry had years ago for diabetic retinopathy—and cousin Harry ended up losing his vision from the diabetic retinopathy. Other patients may equate it with LASIK horror stories they've read about on the Web.

Unfortunately, this means that in many cases there has to be a fair amount of educating by the physician. Some doctors do take the time to educate uninformed patients about the procedure, but a lot of doctors, with their time and energy already stretched to the limit, don't want to be burdened with this. So when they sense the reluctance of a patient regarding the laser, they often just choose to exhaust the medication options before resorting to it.

Another patient-attitude issue that affects the use of SLT is that the public has been taught in some ways to question the medical system. Some people aren't convinced that doctors know what they're doing, or are concerned that a doctor may be pushing an option for his or her personal gain. They may think the surgeon wants to use the laser because he can make more money by doing so than by prescribing medications. Doctors don't like being put in the position of seeming like a salesman, so in some situations that may influence them to opt for prescribing medications, simply to avoid the appearance that the choice was self-serving—especially since laser trabeculoplasty does not subjectively improve a patient's vision.

Tony Realini, MD

A resident receives selective laser trabeculoplasty as part of a study in St. Lucia.[2] The study demonstrated SLT's effectiveness as an alternative to medical glaucoma treatment.

For all these reasons (and possibly others) there may be a reluctance on the part of doctors to push SLT too far to the forefront of treatment options. Exhausting reasonable medication options before resorting to the laser is simply more acceptable to many patients who don't know much about laser trabeculoplasty.

Given the problems associated with medication use, this is ironic. Doctors understand the issue, however; if you ask a group of doctors whether they'd start with laser or medications to treat their own glaucoma, quite a few will choose the laser.

Patient Adherence

Medications may work well for managing glaucoma—and they may appear to be working well when patients come in to see us because the patients have used the medication before the visit—but if patients are not using their medications every day, we're not going to achieve our goal of preserving vision.

Certainly one of the great advantages of laser trabeculoplasty is that it eliminates problems with patient adherence. Even in the old days doctors knew that questionable patient adherence was a problem, but we tended to hope for the best. These days I think it's clear that we can't continue with that attitude, because people are still losing vision on our watch. One reason is lack of compliance using medications.

Of course, other alternatives can also help to address this issue, including using trabeculectomy as primary treatment, or implanting a shunt. Another exciting area that hasn't fully blossomed yet is alternative drug delivery; we may be able to use contact lenses, punctal plugs or intraocular injection to deliver medications, eliminating the patient compliance issue. I think there's every intention on the part of physicians to find ways to keep pressure lowered without depending on eye drops. At the moment, however, one of the best and least-risky options for doing that is laser trabeculoplasty.

Helping the Community

Because SLT avoids the issue of patient compliance, it's a particularly good option for treating individuals in communities that are underserved and unlikely to support the continuous use of medications. In that spirit, our clinic is currently involved in a Centers for Disease Control and Prevention public health program, a pilot screening initiative in Philadelphia. We're reaching out to high-risk underserved populations with mobile units. We send a team of medical personnel with all of the equipment necessary to do a complete eye exam, including visual fields, slit-lamp exam and optic nerve photography, and engage individuals in a multi-step process.

The first step is an educational component in which participants go to a senior center in an African-American neighborhood. Everybody attends a lecture on glaucoma explaining what it is and how it's treated. We talk about laser as well as medication; it's not a long program and it's very basic. After that, we've had virtually 100 percent follow-up in terms of people wanting

to attend the glaucoma screening. After the screening, patients identified as having glaucoma are offered the option of receiving laser or medical therapy right on the spot, and many choose laser as the first therapy. That supports the idea that a patient's decision about the laser may hinge on understanding what laser therapy is, how it works, and the risk profile associated with laser and medications.

The value of this kind of effort has been well-demonstrated in the St. Lucia study, recently published by Tony Realini, MD, associate professor of ophthalmology at West Virginia University Eye Institute in Morgantown, W.Va.[2] In this study, 61 individuals of African descent in St. Lucia who were being medically treated for primary open-angle glaucoma underwent a 30-day washout followed by bilateral 360-degree SLT. All eyes showed a sustained response to the therapy even at one-year follow-up; 78 percent had at least a 10-percent reduction in pressure from the post-washout level; and 93 percent of successful subjects had IOP levels lower than the levels they'd achieved with medication. This certainly supports the idea that SLT can be a big help in communities that don't necessarily have the means to support chronic medical therapy.

SLT won't be effective for everybody, and it's not going to work forever (although it may be repeatable). But if you treat people in the community who are high-risk—especially if they're relatively young—you're at least starting them off on a good footing. That one step could be very helpful for the population as a whole.

From the perspective of a public health official, I would see this as being akin to using fluoride in drinking water. On a smaller scale, that's what we're trying to do with the CDC project in Philadelphia. But whether you're helping underserved individuals in the community or managing patients in your clinic, a treatment that's effective and avoids the problem associated with patient adherence is a powerful tool to have in your armamentarium. REVIEW

Dr. Katz is the director of the Glaucoma Service at the Wills Eye Institute in Philadelphia. He has received past research grants from Lumenis.

1. Katz LJ, Steinmann WC, Kabir A, Molineaux J, Wizov SS, Marcellino G; SLT/Med Study Group. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: a prospective, randomized trial. J Glaucoma 2012;21:7:460-8.
2. Realini T. Selective laser trabeculoplasty for the management of open-angle glaucoma in St. Lucia. JAMA Ophthalmol. 2013;131:3:321-7.

A Primer on Cortical Visual Impairment

We owe the parents of children with CVI a better explanation of their child's condition. Here's a look at how to start providing one.

Sharon S. Lehman, MD, Wilmington, Del.

Parents of children with cortical visual impairment deserve more of an explanation of their child's condition than, "The eye examination is normal. No glasses are necessary." In the past, eye-care providers, including ophthalmologists, were often uncomfortable when dealing with the patient and family with a complex set of challenges. There was a perceived dismal prognosis with no hope of recovery. Cortical visual impairment, which is already the most common cause of vision loss in children in developed countries, will increase in incidence as medical technology and research continue to improve survival.[1] Better information and more tools can assist the ophthalmologist in providing patients with care.

Definition & Characteristics

Cortical visual impairment is defined as bilateral visual impairment, involving acuity and/or higher visual functions, such as visual motor planning, due to posterior visual pathway disease. It is one component of a global neurologic process.

Patients with cortical visual impairment often display characteristic behaviors that may improve or resolve as the child improves. These characteristics include: light gazing; photophobia; poor visual attention; preferences for certain colors; visual field abnormalities; difficulty with visual complexity; problems with viewing distance; eccentric viewing; atypical visual reflex behaviors; and variability with contrast.[2] These characteristics may resolve as a patient improves. A detailed history may reveal previously present characteristics.

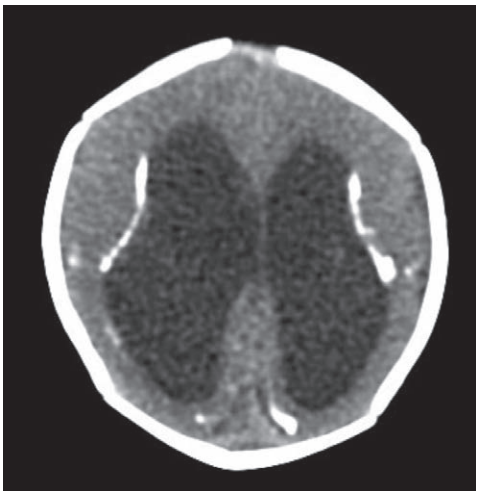


Figure 1. Axial CT scan illustrating hydrocephalus with volume loss and damage to optic pathways resulting in cortical visual impairment.

Causes

Sean P. Donahue, MD, PhD, and colleagues have demonstrated that the most common causes of cortical visual impairment in children are perinatal hypoxia, prematurity and hydrocephalus.[3] Other etiologies in children and adults include: traumatic brain injury; stroke; congenital anomalies; central nervous system infections; neonatal hypoglycemia; and seizures.[4]

These patients may have comorbidities and associated deficits that make the identification, evaluation, treatment and rehabilitation of the patient more difficult. R. Michael Siatkowski, MD, and colleagues have shown that premature infants are particularly vulnerable to anterior and posterior visual pathway disease, which may complicate the identification of the cause of vision loss.[5]

This article has no commercial sponsorship.

Pathophysiology

Melvyn A. Goodale, PhD, and A. David Milner, PhD, described the two-stream hypothesis of neural processing in 1999. Information concerning recognition of objects travels from the occipital cortex to the inferior temporal cortex (ventral stream). Information concerning the location of objects and control of movements to locate objects in space travels from the occipital lobe to the parietal lobe (dorsal stream).[6] Pathophysiology affecting the ventral stream may cause difficulty with object and facial recognition. Pathophysiology of the dorsal stream may cause difficulty locating objects and visual motor planning (visual guidance of movements).

Originally, it was thought that these two systems were separate entities; however, more recent research indicates that processing of complex visual information requires connections between the ventral and dorsal streams.[7]

Classroom learning is largely vision-based. Both ventral and dorsal stream pathology may hinder educational progress, unless accommodations and interventions are made. Activities of daily living are also highly dependent on vision. A child's independence in routine activities may also be affected and require deficit-based compensation.

Periventricular leukomalacia and perinatal stroke make premature infants particularly vulnerable to visual pathway damage, resulting in the previously described typical visual characteristics associated with cortical visual impairment. Visual performance often mirrors the global neurologic deficit. More severely affected patients with quadriplegic cerebral palsy often have more limited visual performance. Patients with diplegic cerebral palsy may have better visual acuity and performance but may demonstrate visual field deficits and higher-level function deficits.

Classification and Prognosis

Christine Roman-Lantzy, PhD, has described a spectrum of phases that correlate with the severity of visual characteristics displayed by a patient with cortical visual impairment. Phase I is the lowest level of function, where a patient displays minimal visual responses. Phase II is a higher level where visual performance is linked to improved function. Phase III is the highest level of performance, where some typical characteristics may become extinct.[8] Patients may progress from one phase to another with improvement in function. This type of classification provides a common language for families and the multidisciplinary team caring for a child. It is also the basis for providing interventions and accommodations that may be used to assist a patient with cortical visual impairment in the educational setting and with activities of daily living.

Baseline visual acuity at diagnosis cannot be used to predict final visual performance. The degree of damage demonstrated on brain imaging studies cannot be used to predict final visual performance either.

In the past, cortical visual impairment was called cortical "blindness," with a perceived poor prognosis. Although some patients may not have any improvement, studies have shown that the majority of patients have at least some improvement in vision.[9] It is important to communicate this fact to families when the diagnosis of cortical visual impairment is made.

It is important to educate families as well as other health-care providers who may treat children with cortical visual impairment in order to prevent inaccurately poor prognostic predictions. Baseline visual acuity at diagnosis cannot be used to predict final visual performance. The degree of damage demonstrated on brain imaging studies cannot be used to predict final visual performance either.

The Ophthalmologist's Role

The ophthalmologist is an important member of the multidisciplinary team that cares for a child with cortical visual impairment.

During the history taking, it is important to solicit observations of visual performance from the family and other members of the child's care team. A child's performance in a limited examination time, in an unfamiliar place when he may be tired and hungry, may not be representative of true function. It is often the occupational or physical therapist who first notes a visual field defect in a patient.

A full ophthalmologic examination, including cycloplegic refraction, should be performed in order to assess visual acuity, look for characteristics of cortical visual impairment, and identify the presence of clinically significant ocular conditions. Visual performance can be maximized by treating any ocular comorbidities, including any significant refractive errors. Dynamic retinoscopy is a useful tool to evaluate for accommodative insufficiency.

Table 1. CVI Internet Resources

1. American Printing House for the Blind
aph.org/cvi

2. American Foundation for the Blind
afb.org

3. American Association for Pediatric Ophthalmology and Strabismus
aapos.org

4. Little Bear Sees
littlebearsees.org

It is vital for the ophthalmologist to make and document the diagnosis of cortical visual impairment, as well as reduced visual acuity, if present. Patients may qualify for services based on the level of visual impairment, especially if a patient has a chronic visual condition that will impair educational progress. Further assistance for interventions or accommodations that may help a patient reach his or her full potential depends on the diagnosis made by the ophthalmologist.

When appropriate, a referral for an evaluation for vision services from the appropriate agency should be made. The referral for infants and children prior to the third birthday can be made through their early intervention program or appropriate state agency, depending upon the patient's state of residence. The referral for children age 3 and older is made through the school district or appropriate state agency.

The findings of the eye examination and diagnosis should be discussed with the family. Educational and resource materials should be provided. It is important to provide a list of websites with accurate information appropriate for the patient's diagnosis, since many families primarily use the Internet for medical information. It is also helpful to have pre-printed information ready to give families whose child has a common diagnosis.

Specific recommendations for treatment, interventions and accommodations should be discussed with families, documented and given to families in writing as part of the discharge instructions.

Recommendations for interventions and accommodations should be based on the patient's level of function and characteristics of impairment present. Suggestions for a low-functioning, 6-month-old, former preemie with periventricular leukomalacia and hypotonia in Phase I may include:

1. High-contrast, lighted and moving visual stimuli;
2. Avoid overstimulation;
3. Provide support for body when performing visual tasks;
4. Allow extra time for response to visual stimuli; and
5. Use auditory and tactile cues to attract and sustain visual attention.

Suggestions for a higher-functioning, school-age child with cerebral palsy in Phase III may include:

1. Allow extra time for response to visual stimuli because of processing and expressive delay;
2. Limit complexity and increase as tolerated;
3. Avoid graphite pencil on recycled paper;
4. Use black marker on white paper for written activities; and
5. Exploit auditory learning skills.

Children with a disability that interferes with educational progress who attend school accepting federal funds may qualify for an individualized educational plan, or IEP, under the Individuals with Disabilities Education Act (See idea.ed.gov.) It is important to document these needs and communicate appropriately with the family and other members of the child's multidisciplinary team.

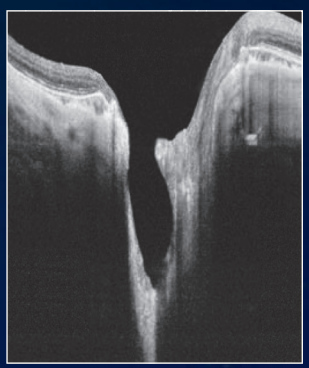
It is imperative for the ophthalmologist to be an active and involved member of the team caring for a child with cortical visual impairment. The ophthalmologist should provide diagnoses, referrals for services, treatment of ocular co-morbidities, education and advocacy for the patient. Interventions and accommodations allow the child with cortical visual impairment to attain his or her fullest educational potential and maximize independence in activities of daily living. REVIEW

Dr. Lehman is the chief of ophthalmology at Nemours/AI duPont Hospital for Children, Wilmington, and a clinical professor of ophthalmology and pediatrics at Jefferson Medical College/Wills Eye Institute, Philadelphia.

1. Good WV, Jan JE, de Sa L, Barkovich AJ, Groenveld M, Hoyt CS. Cortical visual impairment in children. Surv Ophthalmol 1999;38:351-364.
2. Roman C, Baker-Nobles L, Dutton GN, et al. Statement on cortical visual impairment. JVIB 2010;104:69-72.
3. Khetpal V, Donahue SP. Cortical visual impairment: Etiology, associated findings, and prognosis in a tertiary care setting. J AAPOS 2007;11(3):235-239.
4. Soul J, Matsuba C. Visual Impairment in Children Due to Damage to the Brain. In: Dutton GN, Bax M, eds. Causes of damage to the visual brain. London, England: Mac Keith Press; 2010:20-26.
5. Siatkowski R, Good W, Summers C, Quinn G, Tung B. Clinical characteristics of children with severe visual impairment but favorable retinal structural outcomes from the Early Treatment for Retinopathy of Prematurity (ETROP) study. J AAPOS 2013; 17(2): 129-134.
6. Goodale MA, Milner AD. Separate visual pathways for perception and action. Trends Neurosci 1992 Jan;15(1):20-5.
7. Wang J, Zhou T, Qiu M, Du A, et al. Relationship between Ventral Stream for Object Vision and Dorsal Stream for Spatial Vision: An fMRI+ERP Study. Human Brain Mapping 1999;8(4):170-181.
8. Roman-Lantzy C. Cortical visual impairment: An approach to assessment and intervention. New York: AFB Press; 2007.
9. Huo, Richard, Susan K. Burden, Creig S. Hoyt, and William V. Good. Chronic cortical visual impairment in children: Aetiology, prognosis, and associated neurological deficits. Brit J Ophthalmol 1999;83:670-675.

Save the Date!

Clinical Advantages of Swept Source OCT and New Non-Damaging Laser Treatments



Date: **Sunday, November 17th**

Time: 5:30 pm Registration, Cocktails & Hor d'oeuvres
6:00 pm Presentation

Venue: **W New Orleans**
Great Room
333 Poydras Street
New Orleans, LA 70130
Phone: 504-525-9444

Speaker	Affiliation	Presentation Title
Robert Weinreb, MD	University of California San Diego	*"New Swept Source OCT for Glaucoma: Improvements and Advantages"*
Richard Spaide, MD	Vitreous, Retina, Macula Consultants of New York	*"OCT Imaging of the Choroid and Beyond"*
Paulo Stanga, MD	Manchester Royal Eye Hospital	*"Clinical Efficacy of Non-Damaging Treatment Options with PASCAL Laser"*

3 Ways to Register!*

Online: www.revophth.com/OCTnov17
Call: 866-730-9256
Email: ReviewMeetings@Jobson.com

Supported by

TOPCON
CONNECTING VISIONS

Sponsored by

REVIEW of Ophthalmology

This event is not affiliated with the official program of the Joint Meeting.
Please refer to your state laws for any attendance restrictions. Attendance at this event is limited to eye care professionals. Due to individual state legislation, physicians from Minnesota, Vermont and Massachusetts may not attend this symposium.

*Registration is Complimentary

When LASIK Pain Won't Go Away

Tips for diagnosing and managing a rarely seen but debilitating adverse event associated with the LASIK procedure.

Walter Bethke, Managing Editor

The virtually pain-free nature of LASIK is one of reasons it's become the most popular form of corneal refractive surgery. However, there may a very small subset of LASIK patients who don't enjoy this benefit after the procedure; instead they suffer from constant eye pain postop, and turn to the ophthalmologist for help. Here, experts on pain in general and post-LASIK pain specifically discuss this rare phenomenon and how to respond if a patient experiences it.

Patient Presentation

Steven Wilson, MD, a surgeon at the Cleveland Clinic's Cole Eye Institute, says he started to realize something was different about a small number of patients who were being referred to him. "I've only had three patients who I've thought had it," he says. "They had been to three or four physicians and never seemed to be able to get relief. These were patients who seemed to have discomfort in their eyes that was way out of proportion to any of my findings in their eyes. There was no inflammation and the pain didn't resolve after any existing dry eye was treated. They complained of a chronic aching in the eye, and also noted that the pain wasn't intensified by pressing on the eye through the lid or any such tests."

As Dr. Wilson alluded to, since some patients with LASIK-induced neurotrophic epitheliopathy, or LINE, can also have ocular discomfort, the clinician first has to rule out this condition when faced with a patient with chronic eye pain. "Most LINE patients don't have eye pain," he says. "Because, in most, the flap is numb until many months after the LASIK surgery. So, they may have a lot of punctate epithelial erosions on the surface of the cornea but not feel any discomfort whatsoever.

"However, what these LINE patients do have is fluctuating vision," Dr. Wilson adds. "That's the main symptom of LASIK-induced neurotrophic epitheliopathy. The patient with LINE may have a little discomfort at the flap edge where he still has some innervation, but it's not this type of pain. This chronic, non-LINE pain that patients rarely complain of is very bothersome, and may even interfere with sleeping, for instance. These are the kinds of complaints that you just don't hear with LINE."

Solving the Problem

Dr. Wilson says his research into this type of pain makes him think it's closer to complex regional pain syndrome, an entity that is known to strike anywhere in the body, and is more common after severe injuries. However, there appear to be some differences in CRPS in the eye vs. other locations.

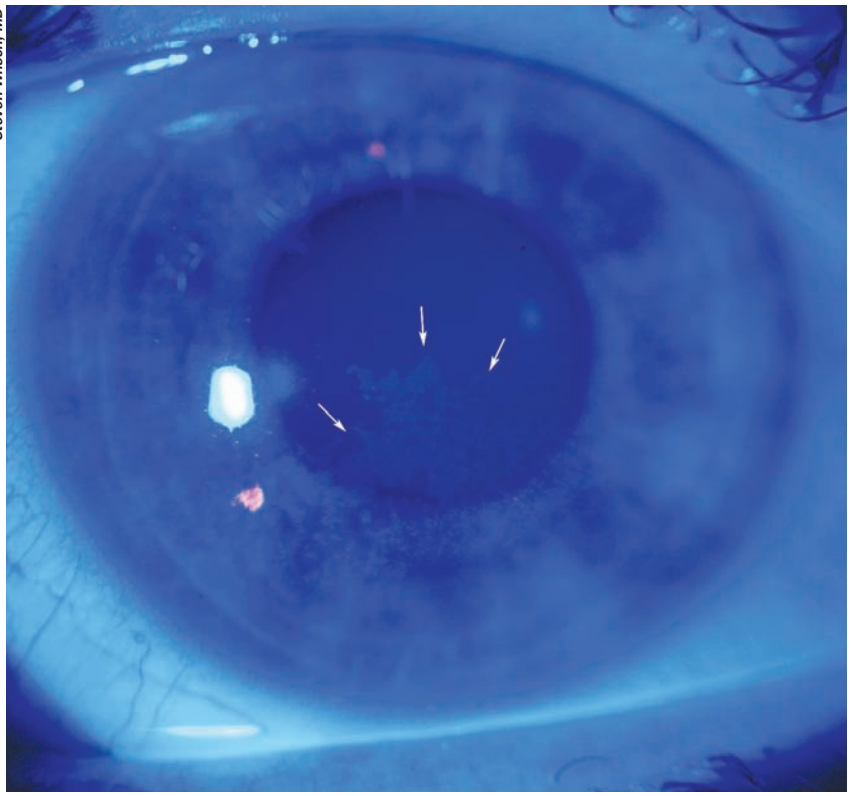
"Chronic pain is more likely to occur not after surgery but after other trauma," says pain specialist Michael Stanton-Hicks, MD, Dr. Wilson's colleague at the Cleveland Clinic. "Probably 70 percent of such pain is related to nerve injury, either metabolic, traumatic or infective. The other major source of it in the United States is failed back surgery. It's a completely different animal compared to acute pain, which is a normal physiologic response to some type of injury. Chronic pain is a total reset of the nervous system to a chronic focus on whatever the start of the pain was. If it continues for longer than three months,

then it's chronic."

In Dr. Wilson's LASIK patients, the cutting of the LASIK flap may have been enough trauma to touch off a chronic pain type of response. "I think it comes from some type of abnormal regeneration of the nerves that get cut when you make the LASIK flap," he says. "In most patients, these nerves grow back perfectly normally; they may not have the same density in some people after their LASIK procedures, but they don't have pain. But, in the very rare patient, for whatever reason, they get a chronic pain syndrome."

To make a definitive diagnosis and start a treatment regimen, Dr. Wilson says you first have to get rid of any LINE. "LINE is very responsive to anti-inflammatory treatment with topical cyclosporine, presumably because in addition to the neurotrophic component, patients also have some underlying inflammatory dry eye," he explains. "So, when you treat that inflammation, their overall condition gets better. You wouldn't normally think of cyclosporine as being a medication that affects the neurotrophic component, though there have been some reports on how it can be a trophic factor for nerves, so you can't exclude it completely on that count. But I think for many of the patients who get LINE, LASIK was the final stressor that tipped the ocular surface over the edge; they actually had a baseline, underlying inflammatory dry eye that may have been so mild you didn't even see it at the slit lamp prior to surgery. But, when you did the LASIK, that was the added stressor that gave rise to punctate epithelial erosion. So, by treating that underlying dry eye, a lot of them will get better. And, even if you don't treat the neurotrophic component, usually by six to eight months after surgery, when the nerves have regenerated back into the flap, it gets better on its own."

Steven Wilson, MD



LASIK-induced neurotrophic epitheliopathy can cause some ocular discomfort and, as such, must be eliminated as a diagnosis before the physician can determine if a patient has chronic pain. This LINE case resolved with treatment within two weeks.

However, in the rare patient with chronic pain, resolving the dry eye doesn't help, and Dr. Wilson says that's when you need to get a pain expert involved, in anticipation of starting more serious medications. "You basically will come to a point where you've gotten the dry eye better but the patient still has the ocular discomfort," he says. "But they do respond to Neurontin, Lyrica or other medications in that class. When they begin to feel better with these drugs, that's the best indication that you've got the right diagnosis of chronic pain.

"All three of the patients I treated required different dosages of pain medication," Dr. Wilson adds. "That's why, in my opinion, it's important to get a pain management specialist involved, because he or she will be used to prescribing those types of medications. When the patient starts on one of these agents, you gradually increase it: You start with the minimum dose and the patient stays on it for several days; if he still has pain, you go a little higher on the dose. You keep increasing it until the pain is controlled, then stay at that dose."

Dr. Wilson says that, though the drugs have been effective, there are some side effects to keep in mind. "These drugs do have some side effects, such as an increase in appetite that can lead to weight gain," he says. "You can also have all kinds of anticholinergic symptoms such as GI distress or diarrhea, though none of the patients I treated successfully had any of those types of things." REVIEW

Elevated Immune Mediators in BSRC

A single-center, prospective, case-controlled study at the Massachusetts Eye Research and Surgery Institution discovered that patients with birdshot retinochoroidopathy with active disease naïve to systemic therapy have elevated serum levels of three key immune mediators known to promote T helper 17 cells in autoimmune disease: interleukin-21, IL-23 and transforming growth factor-β1. These results suggest that IL-21, IL-23 and TBF-β1 may play an important role in the development of site-specific Th17 cell-mediated inflammation in BSRC.

The serum of 17 BSRC patients was analyzed during different phases of disease activity and therapy, with a quantitative multiplex sandwich enzyme-linked immunosorbent assay-based microarray performed to determine the levels of 20 immune mediators (T cell and proinflammatory). The serum of 12 healthy volunteers was used as controls.

Patients with BSRC and active disease naïve to systemic therapy had elevated serum levels of IL-21 (p=0.0005), IL-23 (p=0.0005) and TBF-β1 (p=0.0011) compared to that of controls. There was no significant difference in the serum levels of immune mediators between control and BRSC patients who had a current or past history of IMT or who were in remission. The levels of IL-21, IL-23 and TBF-β1 were positively correlated (IL-23/IL-21 r:0.91; TBF-β1/IL-21 r:0.97; TBF-β/IL-23 r:0.87; for all, p<0.0001).

Am J Ophthalmol 2013;156:400-406.

Yang P and Foster CS.

Brinzolamide-Brimonidine Fixed-Combination Trial Data

This Phase III, double-masked study, set across 66 academic and private practice sites, provides evidence that the investigational non-beta-antagonist fixed combination of brinzolamide 1% and brimonidine 0.2% can safely and effectively lower intraocular pressure in patients with open-angle glaucoma or ocular hypertension. Additionally, the fixed combination shows significantly superior IOP-lowering activity compared with either brinzolamide or brimonidine monotherapy while providing a safety profile consistent with that of its individual components.

A total of 660 adults with a clinical diagnosis of open-angle glaucoma or ocular hypertension from a referred sample were enrolled. Patients were randomized 1:1:1 to treatment with fixed-combination brinzolamide 1% and brimonidine 0.2%; brinzolamide 1%; or brimonidine 0.2%, one drop a day, three times a day for three months. Mean IOP was measured during the three-month visit at four time points: 8 a.m., 10 a.m., 3 p.m. and 5 p.m.

Baseline mean IOP values were similar among treatment groups at all four time points. At three months, the mean IOP of the brinzolamide-brimonidine group (16.3 to 19.8 mmHg) was significantly lower than that of either the brinzolamide group (19.3 to 20.9 mmHg; $p \leq 0.002$) or the brimonidine group (17.9 to 22.5 mmHg; p<0.001) across all time points. One out of 10 serious adverse events (chest pain, brinzolamide group) was judged as treatment-related. A total of 129 patients experienced at least one treatment-related adverse effect (brinzolamide-brimonidine, 22.9 percent; brinzolamide, 18.6 percent; and brimonidine, 17.3 percent; p=0.31), most of which were ocular.

JAMA Ophthalmol 2013;131:6:724-730.

Katz G, DuBiner H, Samples J, Vold S, et al.

Liquid Culture Media for Diagnosing Microbial Keratitis

Researchers from the L.V. Prasad Eye Institute in India conducted a retrospective review of the microbiology records of 114 corneal scraping samples from infectious keratitis patients and determined that liquid culture media increases the chance of isolation of bacteria in pure bacterial and/or mixed infection. However, the role of liquid culture in isolating fungus is limited. Due to the overlap in clinical diagnosis

CPE
OPHTHALMOLOGY
Continuing · Professional · Education

SAVE THE DATE

2013 CALENDAR

CONTINUING PROFESSIONAL EDUCATION

The Continuing Professional Education (CPE) Ophthalmology programs are CME activities designed to complement third-year ophthalmology residency medical education as well as Glaucoma fellows programs. These CME programs take place in a comfortable arena for residents and fellows to exchange ideas with their peers. Faculty for these educational programs are comprised of physicians from both university programs and private practices. The format of the programs consists of presentations of illustrative and unusual cases, panel discussions, and didactic lectures as well as a state-of-the-art, hands-on wet lab experience. It is our hope that you will encourage selected residents and fellows to attend these educational programs, which are all accredited to ensure fair balance.

September 27-28, 2013
Fort Worth, TX

Course Director:
Anthony C. Arnold, MD
Professor & Chief, Neuro-Ophthalmology Division, Jules Stein Eye Institute, Department of Ophthalmology University of California, Los Angeles

GLAUCOMA FELLOWS

October 18-19, 2013
Fort Worth, TX

Course Director:
Kuldev Singh, MD
Professor of Ophthalmology and Director ofGlaucoma Service at the Stanford University School of Medicine, California

For more information and to register

Online: www.revophth.com/ResFellowEdu2013

Email: ReviewLogistics@Jobson.com Call: Denette Holmes 866–627–0714

There is no registration fee for these activities. Air, ground transportation in Fort Worth, hotel accommodations and modest meals will be provided through an educational scholarship for qualified participants.

These activities have been approved for *AMA PRA Category 1 Credit(s)™*.

Jointly sponsored by:

REVIEW of Ophthalmology

NRJ

Supported by an independent medical educational grant from:

Alcon

CME

of bacterial and fungal keratitis, the researchers recommend inclusion of both solid and liquid culture media in the laboratory diagnosis of nonviral keratitis.

Patient samples were processed by corneal smear microscopy (potassium hydroxide with calcofluor white and Gram stains) and culture examination (5% sheep blood agar, sheep blood chocolate agar, Sabouraud dextrose agar, brain heart infusion, thioglycolate broth and Robertson's cooked meat broth). Cases where at least one liquid medium was taken were included in the study and all cases were required to have significant growth in culture as per the institutional criteria. Results of smear examination and culture growth were analyzed.

Out of 114 cases, 44 (38.59 percent) were bacterial, 62 (54.38 percent) fungal and eight (7.01 percent) were mixed bacterial and fungal infection. Thirty-eight of 44 cases of bacterial keratitis (86.36 percent) were diagnosed by solid media alone (criterion 1), while six of 44 cases (13.63 percent) required liquid media for diagnosis ($p<0.001$). In patients with fungal keratitis, 61 of 62 cases (98.38 percent) were diagnosed using solid media alone (criterion 1) while one case required liquid media for diagnosis. In mixed infections, none of the cases required liquid media for diagnosis of the fungal component; however, all eight cases required liquid media for establishing a bacterial component.

Am J Ophthalmol 2013; 10.1016/j.ajo.2013.05.035.
Bhadange Y, Sharma S, Das S, Sahu S.

Fellow Eye Comparison of PK And DSEK in Fuchs Patients

Researchers at the Wills Eye Institute in Philadelphia undertook a retrospective review of patients with Fuchs endothelial dystrophy who had undergone penetrating keratoplasty in one eye and Descemet stripping endothelial keratoplasty in the fellow eye, determining that final visual outcomes were not statistically significant between the two procedures. However, DSEK had early visual stabilization while PK had a more complicated course, with more astigmatism, rejections, suture-related infections and graft failures.

Over an 18-year period, 15 patients with Fuchs underwent PK in one eye and DSEK in the fellow eye. Mean postoperative best-corrected visual acuity in the PK (0.39 ±0.39 logMAR) and DSEK groups (0.23 ±0.12) was statistically significantly better than the mean preoperative BCVA (0.83 ±0.36 and 0.76 ±0.34 logMAR, respectively; $p<0.025$ and $p<0.001$). Mean manifest refraction cylinder was higher in the PK eyes than the DSEK eyes at one year (3.58 ±1.82 D vs. 1.23 ±1.63 D) as well as at two years of follow-up (3.57 ±1.82 D vs. 1.05 ±1.18 D; $p<0.001$) but was not statistically different at the last visit (3.18 ±2.67 D vs. 1.5 ±1.66 D; $p=0.052$). Mean postoperative follow-up was 101.9 ±39.5 months after PK and 29.9 ±19.9 months after DSEK.

The most common complications after PK were high astigmatism in 15 eyes, monocular diplopia in seven eyes, posterior capsule opacity in six eyes and secondary glaucoma and graft rejection in five eyes each. After DSEK, secondary glaucoma in three eyes and graft rejection in two eyes were the most common complications.

Cornea 2013;32:1083-1088.
Kosker M, Suri K, Duman F, Hammersmith K, et al.

Orbital Fractures: National Trends and Complications

Using the Nationwide Inpatient Sample (2002 to 2008) database, researchers determined that the number of orbital fractures and associated cost has dramatically increased over the past decade. Acute repair of orbital fractures is common and associated with a longer hospital course, increased cost and a higher rate of complications.

Researchers searched the database for the discharges classified with ICD-9 diagnosis codes of orbital fractures, orbital fracture repair and associated diagnoses. There was a nearly 50-percent increase in the annual number of orbital fracture admissions from 2002 to 2008. Demographics for patients with orbital fractures showed that 68 percent were male, most commonly between 18 and 44 years of age, with 69 percent of the cases at large teaching hospitals. Associated ocular diagnoses included eyelid laceration, commotion retinae and globe rupture.

Approximately 25 percent of patients underwent surgical repair. Surgical patients were younger than nonsurgical patients by approximately 10 years. There was an overall complication rate of 15.8 percent, including: pulmonary complications; diplopia; renal impairment; venous thromboembolism; and wound complications. Orbital fracture repair was associated with approximately one extra day of hospitalization and $22,000 in-hospital charges. The rates of pulmonary, wound and ocular motility complications were significantly higher in patients undergoing orbital fracture repair ($p<0.05$).

Ophthal Plast Reconstr Surg 2013;29:298-303.
Ko M, Morris C, Kim J, Lad S, et al.

REVIEW® of Ophthalmology

Ophthalmic Resources Online

This service allows you to capture needed measures for two meaningful use objectives:

1) electronic transmission of patient prescriptions

2) distribution of patient-specific education materials

ECP Resources and ePrescribing from *Review of Ophthalmology* and Healthcare Resources Online enable you to provide patient education, electronic prescribing and generate reports that allow you to attest for meaningful use incentives; however, determination of your bonus payments from CMS depends on other factors and qualifications specific to your practice.

For More Information, Visit Our MD E-Prescribing Resources Page:

www.revophth.com/MD_Resources_eRX/

Download a QR scanner app. Launch app and hold your mobile device over the code and get ready to view our website.

REVIEW of Ophthalmology online

EVERY MONDAY

E-News You Can Use

Have you been receiving and reading custom e-blasts from *Review of Ophthalmology*? If not, you're missing out on valuable information!

You're a busy practitioner and not surprisingly, your e-mail inbox is often full. Fortunately, when you scan through the sender list, determining which messages to delete and which to save or read, you can feel confident knowing that e-blasts from *Review of Ophthalmology*, a Jobson Medical Information, LLC publication, contain the most current and comprehensive information available in the field to keep you on the cutting edge.

Review of Ophthalmology's online stable of products includes editorial newsletters and promotional information about new products, treatments and surgical techniques, as well as alerts on continuing education courses for ophthalmologists.

- Our FREE weekly e-newsletter, *Review of Ophthalmology Online*, brings you the latest in ophthalmic research, as well as industry news. In an effort to keep eyecare professionals informed, this resource is waiting in your inbox every Monday morning.
- *Retina Online*, our free monthly e-newsletter, is for retina specialists and general ophthalmologists interested in enhancing their knowledge on the topics of retina and related disease diagnosis and treatment, as well as the latest in surgical procedures.

Your time is valuable — and so is your practice. These e-products are the most effective way for you to receive updates on breaking news and research — all just a click away. Don't miss out!

Unfamiliar with our products? Visit www.revophth.com and check out our newsletter archives.

Go to www.jobson.com/globalEmail/default.aspx to sign up for the e-newsletters that interest you.

jmi

Equipment and Supplies

FLORIDA EYE EQUIPMENT
Since 1989

PRE-OWNED OPHTHALMIC EQUIPMENT

Buying and Selling
Pre-Owned Ophthalmic Instrumentation.
Contact Jody Myers at
(800) 336-0410
Fax: 863-666-1311
E-mail: EyesinFL@aol.com
To view current inventory,
Visit www.floridaeye.com
FLORIDA EYE EQUIPMENT
Since 1989

Products and Services

P.M. MEDICAL BILLING AND CONSULTING

SPECIALIZING IN OPHTHALMOLOGY BILLING & CONSULTING

- *National, full service billing to ophthalmologists*
- *Maximum reimbursement is guaranteed*
- *Staff consists of Ophthalmic techs, expert coders & billers*
- *Increased revenue/low denial rate/complete & unrelenting follow up*

We specialize in old, outstanding AR, Practice Management & Credentialing

Contact us at:
pmmedbill@aol.com
or call us toll-free at:
1-888-PM-BILLING
for a free in-office consultation
WWW.PMOPHTHALMOLOGYBILLING.COM

REVIEW® of Ophthalmology

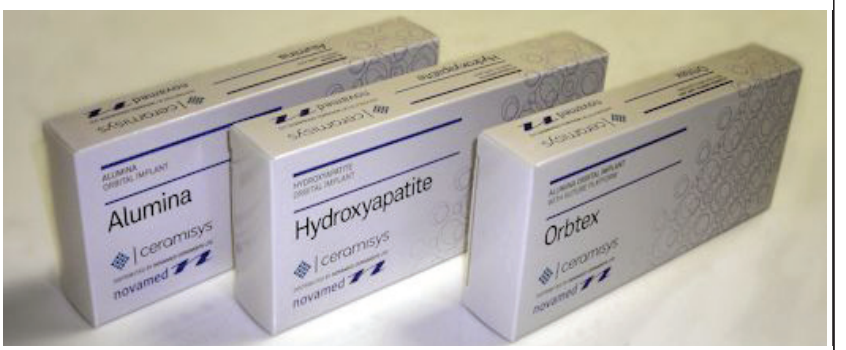
Do you have Products and Services for sale?

Call Today!
Toll free: **888-498-1460**
E-mail: **sales@kerhgroup.com**

Merchandise Offered

Equipment and Supplies

NEW! Bio-Ceramic & Hydroxyapatite Orbital Implants



• Ultra-lightweight and comfortable - over 30% lighter than reported alternative products
• Shorter procedure time • Ultra-porous
• Homogenous and fully-interconnected open network of pores
• High strength and integrity • Non-friable
• Easily drilled for a motility peg

Website search: "Implants"

GuldenOphthalmics
time saving tools
800-659-2250 www.guldenophthalmics.com

For classified advertising
call 1-888-498-1460
or e-mail us at sales@kerhgroup.com

kerh group

Equipment and Supplies

Practice For Sale

ProfessionalOpportunities

Rocky Mountain Eye Center is looking for a **Board Certified or Board eligible General Ophthalmologist** for a seven physician Ophthalmology practice in beautiful Western Montana. This position will be available in 2014 in our busy Butte satellite office. We also have a full time Optometrist at this location. The Rocky Mountain Eye Center has been serving Western Montana for more than 75 years. The main office is located in Missoula with an ophthalmic only surgery center onsite. We also have full time locations in Butte and Hamilton. Subspecialties include surgical retina, glaucoma, oculoplastics, cornea and pediatrics. There is also an optical shop and contact lens department in each location. Butte is an area rich in recreational opportunities with skiing, fishing, hunting, golf, kayaking, rafting and more all in your back yard.

www.rockymountaineye.com
Please contact for further information:
Dr. Roger Furlong at rfurlong@rmeec.com
or Darlene Timmerhoff, Administrator at
timmerhoff@rmeec.com

EquipmentandSupplies

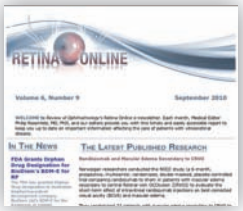
REVIEW® of Ophthalmology

ENRICH YOUR PRACTICE

Review of Ophthalmology delivers current and comprehensive information focusing on topics such as disease diagnosis, surgical techniques and new technologies.

The *Review* Group's *Ophthalmic Product Guide* brings you the latest products and technology on the market. Published every February and July.

The *Review* Group also distributes a variety of supplements, guides and handbooks with your subscription to *Review of Ophthalmology*. These publications are designed to keep you informed on what's new and innovative in the industry on topics ranging from cataract refractive surgery to ocular surface disease.



The *Review* Group also offers valuable Continuing Medical Education sessions in both print and online formats, allowing a convenient way for you to earn CME credits. In addition, we also offer an impressive fleet of free e-newsletters—such as *Review of Ophthalmology Online* and *Review of Ophthalmology's Retina Online*—so you can keep up to date on breaking news and the latest research online.

The Review *Group offers eyecare practitioners quality informational resources dedicated to the growth and education of the profession. The* Review *Group offers a variety of print and online products to enrich your patient care and practice needs.*

The *Review* Group also spearheads meetings and conferences, bringing together experts in the field and providing a forum for practitioners that allows you to educate, and learn from others, in the profession. These meetings cover a broad range of topics in the form of educational or promotional roundtables, CMEs and forums.

www.revophth.com

Jobson Medical Information LLC
***Review* Professional Publications Group**

After a two-year progression of pain in her eye, a woman visits her ophthalmologist. Following an MRI, she is admitted for a craniotomy.

Erin Lally, MD

Presentation

A 54-year-old female presented to her primary ophthalmologist complaining of a two-year history of progressive "pain behind the left eye." The pain was sharp, boring and constant. She denied visual obscurations, visual field loss, double vision or photophobia. An MRI of the brain and orbits revealed a 4 x 4 x 4 cm dural-based mass that arose from the left planum sphenoidale, compatible with a meningioma. The patient was admitted to the hospital for image-guided left pterional craniotomy. The tumor was resected but immediately postoperatively she was no light perception the left eye. In addition, ocular motility in the left eye was decreased 50 percent in down-gaze and adduction.

Medical History

Medical history was significant for degenerative joint disease, a thyroid nodule and breast cancer. The breast cancer was treated in 2006 with bilateral mastectomy and oophrectomy and radiation therapy. The patient took calcium, vitamin D3, a multivitamin, desloratadine and letrozole. She was allergic to sulfa-based medications and intravenous contrast. She was a former smoker.

Examination

Visual acuity at near with no correction was 20/25+ in the right eye and NLP in the left eye. Color plates were full and brisk in the right eye. The right pupil was round and reactive to light and the left pupil was amaurotic. Pupil diameters were equal in the light and dark. Intraocular pressure was 17 mmHg in the right eye and 12 mmHg in the left eye. Motility in the right eye was full but motility in the left eye was consistent with a cranial nerve III palsy. The anterior and posterior exams of both eyes were normal. There was no cherry red spot in the macula and the optic nerves appeared pink and healthy.

Postoperative reports indicated that the tumor was dissected off the orbital apex and there was no clear invasion of the optic canal. The left optic nerve was compressed and displaced laterally by the tumor but there was no frank invasion of the nerve. A thickened pia-arachnoid plane separated the tumor and the left optic nerve.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 76

Before reading on, please see p. 75 for presenting complaint, history and examination.

Diagnosis, Workup and Treatment

A 54-year-old female with chronic periocular headache presented postop day one status post frontal lobe meningioma resection with NLP vision in the left eye and a left-pupil-sparing, third-nerve palsy. The combination of NLP vision and third-nerve deficit localized the process to the posterior orbital apex and optic foramen. This localization, coupled with the mottled fundus appearance, suggested a diagnosis of a left ophthalmic artery occlusion.

One week postoperatively, an OCT of the left optic nerve revealed moderate diffuse thickening *(See Figure 1)*, and the fundus had a homogeneously mottled appearance *(See Figure 2)*. The left third-nerve palsy improved in severity but the patient remained NLP with an amaurotic pupil. The patient was started on taurine and lutein supplements for potential photoreceptor regeneration.

Repeat OCT two weeks postop showed a thinned nerve head and diffusely atrophic inner and outer retinal nerve layers. The left optic nerve was pale and atrophic and the vessels were sclerotic. Three weeks postop, the patient was still NLP but the third-nerve palsy had completely resolved. The taurine and lutein supplements were discontinued.

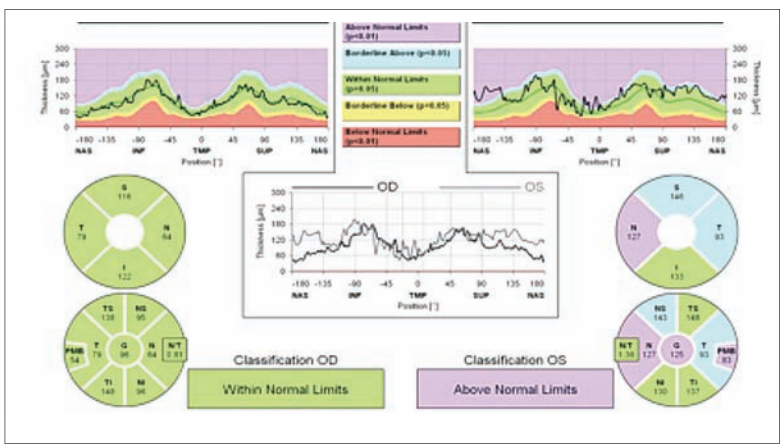


Figure 1. One week postoperative optic nerve OCT of both eyes. There is diffuse swelling of the left nerve head.

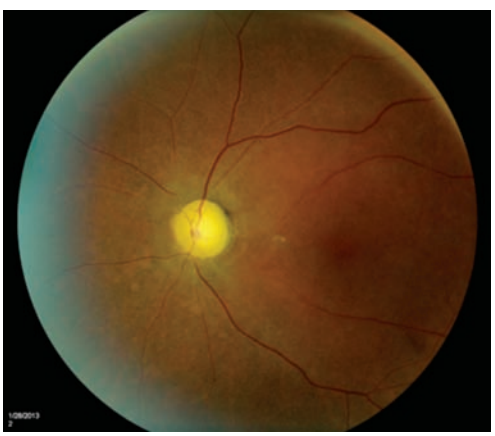


Figure 2. Fundus photography of the left eye postoperative week one. A diffusely pale optic nerve, mottled choroid and sclerotic vessels are noted.

Discussion

Perioperative vision loss after nonocular surgery varies from 0.013 percent to 0.2 percent depending on the type of surgery. It occurs most commonly after cardiopulmonary bypass and spinal surgeries.[1] During cardiac surgery, cholesterol plaques from recannulation of the aorta and microemboli from bypass circuits can infarct distal vessels. In prolonged spine surgeries, patients are often in a prone position, causing increased venous pressure and elevated intraocular pressure, which can result in subsequent ischemic optic neuropathies, cortical blindness and central retinal vein occlusions. Systemic hypotension has also been linked to vision loss. In a retrospective case-review series, patients who developed peri- or postoperative blindness had a decrease in mean blood pressure ranging from 24 percent to 46 percent for 15 minutes for up to two hours.[2]

In our patient, the amaurotic pupil helped localize the process to the visual system anterior to the lateral geniculate nucleus and likely to the retina or optic nerve. Disc edema on OCT suggests a diagnosis of postoperative ischemia, likely secondary to a combination of blood loss, hypotension, hypovolemia and other factors that influence perfusion to the optic disc and cranial nerve III. While operative blood loss was minimal in our patient, her blood pressure was labile, with an average systolic pressure ~100 mmHg.

Most of the blood supply to the anterior portion of the optic nerve comes from posterior ciliary arteries surrounding the optic disc. The main

blood supply to the posterior optic nerve comes from the central retinal artery and pial branches, which are in turn branches of the ophthalmic artery. There is significantly less blood flow to the posterior optic nerve than to the anterior portion.[3] The intracranial optic tract is supplied by branches of the Circle of Willis. Branches of the internal carotid artery and anterior cerebral artery supply the optic chiasm and optic tract, and branches of the middle and posterior cerebral arteries feed the optic radiations and occipital cortex.

A review of ophthalmic pathophysiology illustrates the importance of sustaining adequate blood pressure and hemoglobin levels. Blood flow in the choroid is the highest in the body and flows at a rate of approximately 200 mL/minute per 100 g of blood.[3] Sixty to 80 percent of oxygen that supplies the retina comes from the choroid. Blood flow to the optic nerve can be measured by dividing the perfusion pressure of the globe by the resistance to flow.[4] The perfusion pressure is the mean arterial pressure minus the intraocular pressure. Resistance to flow is varied by autoregulation to maintain a constant blood flow during changes in perfusion pressure. Factors that can decrease perfusion pressure and blood flow include vascular changes; increased blood viscosity; decreased oxygen delivery; overcrowding of the optic disc; and optic nerve edema secondary to nerve fiber layer hypoxia.[5] Venous pressure varies with changes in body position. When the head is lower than the atrium, venous pressure increases and the perfusion pressure decreases. As a result, the choroidal blood flow simultaneously decreases.

Autoregulation operates over a critical range of perfusion pressures to limit risk of ischemic damage.[4] Above or below this range, blood flow is directly dependent on perfusion pressure. Autoregulation is maintained by endothelial-derived vasoactive agents enthothelin-1, thromboxane A2, nitric oxide and prostacyclin.[3] These agents are released abnormally when the endothelium is damaged. Studies have suggested that as ocular perfusion pressure decreases to less than 30 to 35 mmHg, autoregulation is disrupted and the optic nerve may become susceptible to ischemic damage.[4]

Types of perioperative vision loss include retinal ischemia, such as central and branch retinal artery occlusion, and ischemic optic neuropathy, such as anterior and posterior ischemic optic neuropathy. The specific mechanism and location of insult that cause ischemic optic neuropathies remains uncertain. Possible pathogenic factors include prone positioning; external pressure on the eye; long length of surgery; systemic hypotension; blood loss; hemodilution; fluid loss; and use of vasopressors.[5] Uncontrolled blood loss may lead to decreased oxygen delivery to the optic nerve resulting in anterior or posterior ischemic optic neuropathy. The severity and duration of anemia that leads to this complication is unknown, but one study suggests that hemoglobin levels that dip below 8 g/dL for as little as 30 minutes may cause an optic neuropathy.[3]

All patients with postop vision loss need to be seen immediately. These patients should be acutely managed with transfusion of blood, supplemental oxygen and maintenance of normal-to-high systemic blood pressure. REVIEW

The author thanks Robert C. Sergott, MD, of the Wills Eye Institute's Neuro-Ophthalmology Service for his assistance with the preparation of this case.

1. Berg KT, Harrison AR, Lee MS. Preoperative visual loss in ocular and nonocular surgery. Clin Ophthalmol 2010;4:531-46.
2. Brown RH, Schauble JF, Miller NR. Anemia and hypotension as contributors to perioperative loss of vision. Anesthesiology 1994;80(1):222-6.
3. Williams EL. Postoperative blindness. Anesthesiol Clin North America 2002;20(3):605-22.
4. Bansal AS, Hsu J, Garg SJ, Sivalingam A, et al. Optic neuropathy after vitrectomy for retinal detachment: Clinical features and analysis of risk factors. Ophthalmology 2012;119:2364-70.
5. Roth S. Preoperative visual loss: What do we know, what can we do? Br J Anaesth 2009;103 Suppl 1:i31-40. doi: 10.1093/bja/aep295.

(continued from page 5)

and subsequently translate that research into the clinic. Federal grants can provide funding to academics and innovators to advance their programs. In addition, universities have created innovation centers that provide lab space for innovators to conduct research and/or commercialize their findings. Additionally, research incubators are another resource that can help your development program reach a value inflection point in a capital-efficient manner. The current life-science funding landscape is analogous to the Bermuda triangle in that many ophthalmic innovators try to navigate through it and never reach shore. Before setting sail, be sure you have vetted a plan that will guide you to successful milestone achievements. As you work to secure the necessary capital to advance your program to the next value inflection point, this will support the next round of financing.

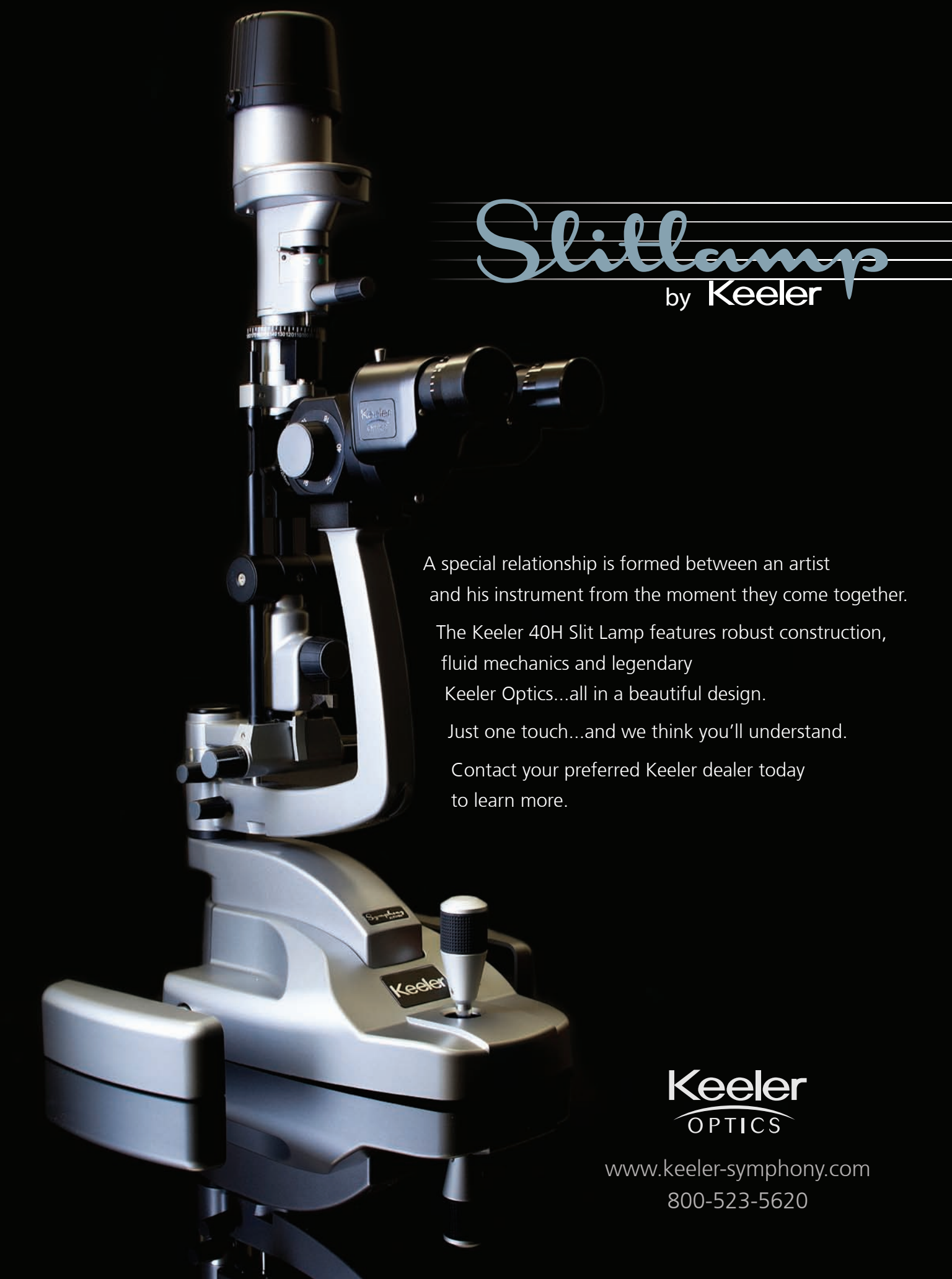
There are a multitude of target investor options, and each has its own has pros and cons. For example, VCs and angel investors can provide capital to fund your program, but their investment will significantly dilute your ownership stake. In addition, they often demand some form of control via board seats to manage their investment. While foundations and grants do not typically dilute your equity stake or demand control of your program/company, the time line to secure funds can be long, the evaluation process uncertain and they often fund very early stage research exclusively. The time it takes to raise funds through grants and foundations may be well-suited to academic innovators who understand the process, have a track record of securing grants and have a day job.

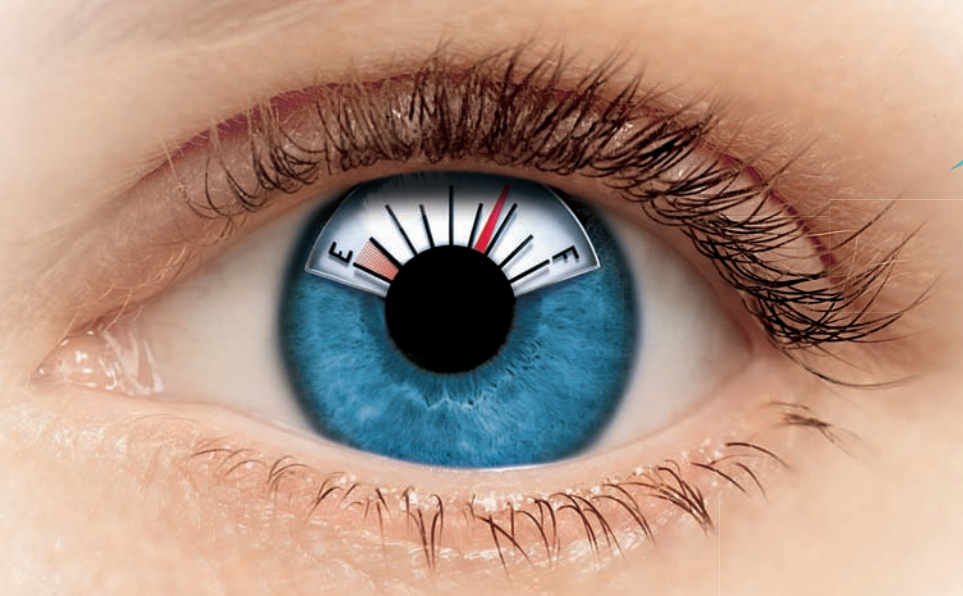
Corporate venture and strategic investors, including CROs and service providers, have grown in prominence and are increasingly providing sources of the necessary capital to support early stage innovation.

In this way, they are ensuring commercial entities have exposure and access to product pipelines and the next generation of ophthalmic products will be there to improve patient care, preserve precious vision and bring sight to the blind.

Mr. Chapin, Dr. Campion and Mr. Sandwick are from the corporate development group at Ora Inc. Ora provides a comprehensive range of product development services and strategic support in ophthalmology.

REVIEW Advertising Index


Slitlamp
by Keeler
A special relationship is formed between an artist
and his instrument from the moment they come together.
The Keeler 40H Slit Lamp features robust construction,
fluid mechanics and legendary
Keeler Optics...all in a beautiful design.
Just one touch...and we think you'll understand.
Contact your preferred Keeler dealer today
to learn more.
Keeler
OPTICS
www.keeler-symphony.com
800-523-5620



Restasis®
(Cyclosporine Ophthalmic Emulsion) 0.05%

restasisprofessional.com

For patients with decreased tear production presumed to be due to ocular inflammation associated with Chronic Dry Eye

RESTASIS® MAKES MORE OF THEIR OWN REAL TEARS POSSIBLE

Prescribe RESTASIS® for your appropriate moderate and severe Dry Eye patients and increase their own real tear production over time with continued use

For local co-pays, scan QR-code or visit restasiscopay.com

Indication and Usage

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Important Safety Information

Contraindications

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

Warnings and Precautions

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, individuals prescribed RESTASIS® should not touch the vial tip to their eye or other surfaces.

Use With Contact Lenses: RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion.

Adverse Reactions

In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

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

ALLERGAN