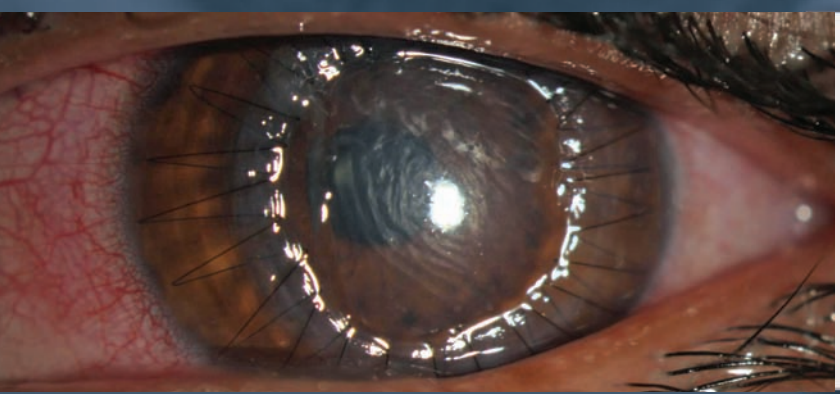
RCCL®
REVIEW OF CORNEA & CONTACT LENSES

OCTOBER 2014

Lamellar Surgery:

The Bold New Look of Corneal Transplants



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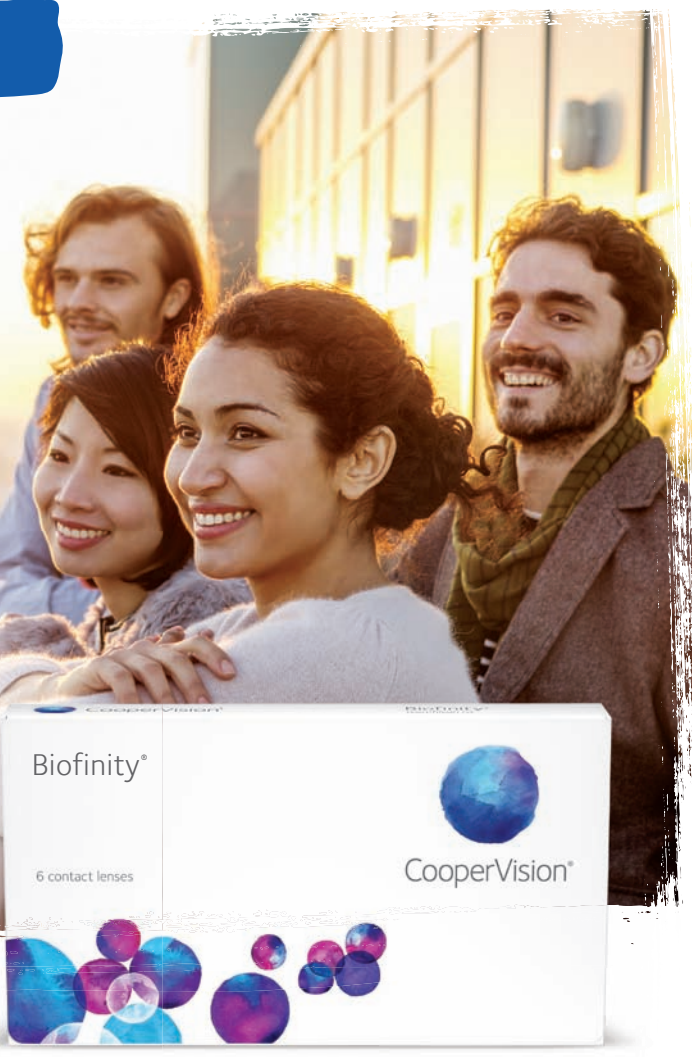

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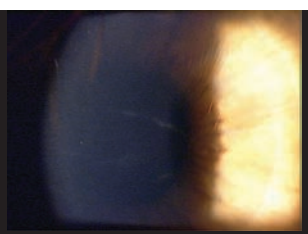
contents

Review of Cornea & Contact Lenses | October 2014

departments

features



Cover design by Matt Egger
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IN BRIEF

• A Phase II clinical study will evaluate topical **cis-Urocanic acid (cis-UCA) to treat dry eye**. Cis-UCA is an endogenous amino acid metabolite derived from histadine, normally present in the human body with particularly high concentrations located in the skin, explains James McLaughlin, PhD, of Ora, a clinical research and product development firm that will oversee the project. It's believed to work as an **anti-inflammatory agent** by reducing PMN cell reactive oxygen species.

Phase I (n=37) evaluated safety, with drops administered TID for 14 days in 0.5% and 2.5% concentrations. Both were well tolerated, with no serious adverse effects. Phase II will randomize **150 dry eye patients** into one of three groups (placebo or one of two dosages of the cis-UCA eye drop). Patients will be evaluated over a five-week period using the Controlled Adverse Environment, a clinical assessment tool developed by Ora. Corneal staining and OSDI scores will be collected during the trial.

If successful, the cis-UCA drop could one day join a very limited group of prescription drugs for dry eye.

•**Acuvue Oasys** silicone hydrogel lenses for astigmatism now come with a new **-2.75 cyl** option, the first SiHy lens to do so, says manufacturer Johnson & Johnson Vision Care. No special ordering is needed, the company says.

• New research published in the October 2014 *Cornea* suggests **collagen crosslinking may be effective in halting keratoconus** progression for up to five years. Twenty-one patients with progressive keratoconus who underwent CLX were evaluated preoperatively and postoperatively at one-year intervals up to five years. Researchers observed mean uncorrected and best spectacle-corrected **visual acuity improved significantly** from the pre-op visit to the five-year postoperative visit. Additionally, mean steep and mean flat keratometry readings dropped significantly in the same time period. **No significant change was observed in endothelial cell density** or mean central corneal thickness.

Who Isn't a Good Candidate for Refractive Surgery?

Unusual corneal topography and insufficient corneal thickness remain the most common exclusion factors for corneal refractive surgery, according to a new retropective study that examined patient criteria for LASIK and PRK, published in the October 2014 *Cornea*.[1]

Researchers from the Cole Eye Institute in Ohio and the University of Sao Paulo in Brazil evaluated 1,067 candidates—519 males and 548 females—for primary refractive surgery procedures over a five-tyear period.

Prospective patients were considered if they met the following general criteria: age 18 years or older, stable refraction for at least one year, myopia ≤10.5D, hyperopia ≤4.50D, astigmatism ≤6.00D, central corneal thickness >480µm measured with ultrasonic pachymetry, expected residual stromal bed >300µm after LASIK, and >400µm corneal thickness after PRK or LASIK. Additionally, prospective patients could not be pregnant or lactating, have corneal abnormalities indicative of keratoconus or other corneal ectatic disease, or exhibit ocular pathology such as an active infection.

Of the initial candidates considered, 61.6% (657 patients) underwent refractive surgery. Based on the criteria, LASIK was selected as the better option for 556 of these patients, while PRK was considered better for 106 patients (e.g., for those with thin corneas, high risk of injury or simple patient preference)

Of the 410 patients who did not undergo refractive surgery, 276 choose to defer the procedure while 134 were deemed medically contraindicated to both LASIK and PRK, with abnormal corneal topography (34.3%) and low or insufficient corneal thickness (23.1%) the most common reasons for exclusion. This is in contrast to previous studies, based only on LASIK surgery with mechanical microkeratomes, which pinpointed insufficient corneal thickness to be the most common reason.

The study also identified cataract (9.7%) and high myopia (10.5%) as other common exclusion factors, as well as high hyperopia (3.7%), the need to wear reading glasses after surgery (3.7%) and severe dry eye unresponsive to treatment (3.7%).

1. Torricelli A, Bechara S and Wilson S. Screening of refractive surgery candidates for LASIK and PRK. Cornea 2014;33:1051-1055.

Hyperosmolarity May Impact Cataract Surgery Plan

A study of 67 cataract surgery patients found that tear hyperosmolarity resulted in a wider variation in keratometry readings between visits than normal osmolar status, with 16% of hyperosmolar eyes showing over 1D of change in K cylinder values between the first and second visit, according to TearLab. The study was presented at the recent Congress of the European Society of Cataract and Refractive Surgeons in London, and will be submitted for publication.

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Chronic Pain May Influence Dry Eye Disease

Women who have dry eye are also more likely to suffer from chronic pain, and the connection may even be part of a previously unknown etiology of the condition, according to new research published in the *British Journal of Ophthalmology*.[1]

Researchers from St. Thomas' Hospital in London and the University Medical Center Groningen in the Netherlands used a questionnaire to collect patient-provided health information on dry eye and related risk factors from 3,824 British women from 2,410 families aged 20 to 87. This marks the first time a population-based epidemiological study on dry eye has been done in the UK.

Of the subjects surveyed, 9.6% had been diagnosed with dry eye by a clinician and were using artificial tear eye drops or gel, and 20.8% reported experiencing dry eye symptoms within the past three months.

The study results indicated dry eye to be most associated with several chronic pain syndromes: pelvic pain, irritable bowel syndrome and fibromyalgia. Patients with these diseases typically exhibit migraine and depression—two psychiatric conditions also strongly linked to dry eye in this study. As the various disorders have been hypothesized to share a common etiology, these findings, say the researchers, raise the possibility that "altered pain perception and psychological and somatization factors influence DED and its symptomatology" and that "DED might be added to this spectrum of disorders."

Osteoarthritis was also re-identified as a risk factor, and researchers suggested the connection could be due to increased pain sensitivity resulting from the progressive joint disease, which may lead those affected to complain earlier of dry eye symptoms.

Additional known risk factors reaffirmed in the study include age-related macular degeneration, glaucoma and immune-mediated diseases such as rheumatoid arthritis, thyroid diseases and allergies. A strong association between atopic disorders like eczema and asthma and dry eye was also noted, as was a connection between fertility problems and the eye disease. Subjects who wore contact lenses and older subjects were also more likely to exhibit dry eye, particularly those over age 60.

1. Vehof J, et al. Prevalence and risk factors of dry eye disease in a British female cohort. Br J Ophthalmol 2014;0:1–6.

Advertiser Index

By Joseph P. Shovlin, OD

Observing Contact Lens Health Week

The CDC offers a helping hand to eye care practitioners. Let's take it!

Currently, there are more than 30 million contact lens wearers in the United States. While nearly every one will have a safe and uneventful experience of lens wear, the practitioners entrusted with their care must approach them as all being potentially at risk for sight-threatening complications such as ulcerative keratitis. With this in mind, the Centers for Disease Control and Prevention (CDC) has been hard at work this past year developing strategies to minimize the complications associated with contact lens wear. This initiative is based on the idea that if consumers are adequately educated, their risk for such complications will significantly drop.

As part of this ongoing effort to bring attention to the important care and maintenance issues associated with contact lenses, the CDC and its partners—the American Academy of Ophthalmology, the American Academy of Optometry, the American Optometric Association, the Contact Lens Association of Ophthalmologists (CLAO), the Contact Lens Society of America, the National Academy of Opticianry (NAO) and the Contact Lens Institute (CLI)—have designated the week of November 17-21, 2014 as the first-ever Contact Lens Health Week. This year's theme is, "You only have one pair of eyes, so take care of them."

THREE PRINCIPLES

The campaign will stress three points: (1) the importance of healthy contact lens hygiene habits;

(2) proper use, care and storage of contact lenses and accoutrement; and (3) the need for regular visits to an eye care provider. The program is primarily targeted at high-risk groups like teens and young adults, but its messages and materials are suitable for all contact lens wearers.

To promote Contact Lens Health Week and encourage patients to practice proper contact lens hygiene throughout the year, the CDC has developed a promotional toolkit for eye care providers, who can take full advantage of the following: (1) CDC Morbidity and Mortality Weekly Report (MMWR) on estimates of the burden of microbial keratitis in the United States; (2) healthy contact lens wear and care messages, which can be disseminated through social media channels; (3) a collection of posters, web buttons and infographics; and (4) campaign materials, including a list of suggestions for campaign promotion and outreach, a web-based resource list, short messages for social media channels, newsletter summaries and a campaign flyer.

The new program coordinator for this ongoing project—CDC health communication specialist Maya Rao, MPH—has also released a list of highlights from the website. Additional key materials on the CDC site that might be of interest to eye care providers and can be easily shared with patients are below:

- ***"Protect Your Eyes."*** This web page (www.cdc.gov/contactlenses/protect-your-eyes.html) provides tips that are essential to the overarching principles of safe and effective contact lens wear.
- ***"Health Promotion Materials."*** Here (www.cdc.gov/contactlenses/materials.html), the CDC hosts a collection of web buttons, posters, podcasts and social media messages to promote healthy lens wear.
- ***"Water and Contact Lenses."*** This page (www.cdc.gov/contactlenses/water-and-contact-lenses.html) explains the dangers of exposing contact lenses to water through swimming, showering or rinsing, and advises lens wearers on how to avoid potential contamination.

Eye care practitioners who provide contact lens care should take full advantage of these wonderful promotional items. Kudos to CDC and partners for their ongoing, noble efforts to promote safe contact lens wear. I trust each and every colleague will help make this a successful campaign!

For more information on Contact Lens Health Week, visit: www.cdc.gov/contactlenses.. RCCL

Note: A special thank you to Amanda MacGurn, MPH, who headed the workgroup this past year and has recently been reassigned at CDC for her skills and exceedingly capable leadership.

What's 'Bugging' Us About Contact Lens Solutions

Could FDA contact lens solution testing procedures introduced earlier this year help curb future *Acanthamoeba* outbreaks?

Consumers trust the FDA to regulate products and keep us safe, and to address any product-related issues should they arise. Following the 2006 *Fusarium* keratitis outbreak and the 2007 *Acanthamoeba* cases, which resulted in voluntary recalls of two contact lens solutions, the Center for Disease Control (CDC) and the FDA initiated investigations into the root cause of these serious ocular infections. Their findings led the FDA to reevaluate solution testing in the following areas:

(1) ***Lens compatibility***—does the solution alter the parameters of the lens?

(2) ***Cleaning efficacy***, determined through the use of Critical Micelle Concentration (CMC).

(3) ***Microbial testing***, with the use of predetermined microbes.

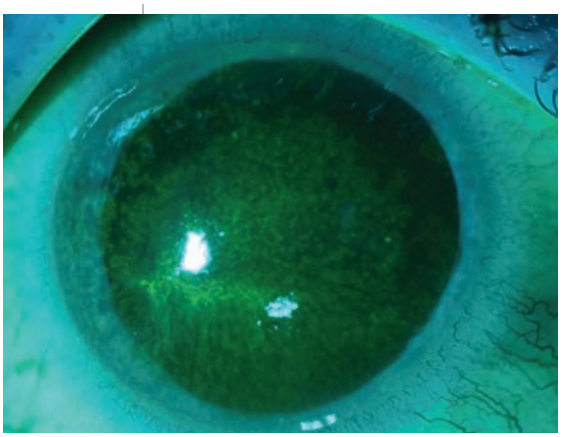
(4) ***Toxicology testing***, to determine cytotoxicity, systemic toxicity and ocular irritation.

(5) ***Clinical testing***, with a minimum of 60 subjects over a period of one month.

In the June 2014 issue, we examined lens compatibility, in particular how materials affect the uptake and release patterns of solution components, and September 2014 we discussed the efficacy of the contact lens cleaning process. This month, we will focus on microbial testing.

AYE, THERE'S THE RUB

Historically, the FDA used two different methods—"rub" and "no rub"—to evaluate microbial efficacy for contact lens solutions. In the "no rub" method, a known cultured organism is exposed to a preset quantity of contact lens solution. If the organism dies as a result of this process, the solution would receive FDA approval for disinfection and could be labeled "no rub," meaning that no rubbing motion is required for the solution to be effective. If a significant amount of organism remains during the "no rub" test, however, then the solution would require a "rub" method.



Dense epitheliopathy and a pseudodendrite on initial presentation of *Acanthamoeba* infection.

In the "rub" method, a lens is exposed to an organism, rubbed and rinsed for five seconds and then cultured for growth. A solution that passes the criteria for this method but does not pass the "no rub" conditions requires the rub and rinse step to be labeled on the packaging.

Unfortunately, neither of these methods took "real-world" factors into account, such as *Acanthamoeba* testing, uptake and release of preservatives, common impurities both in the lens case and on the lens, the effect of the lens case on the solution's composition and patient-related behaviors such as topping off of pre-existing contact lens solution in the case. Additionally, it was not considered that microbe strains repeatedly grown on cultures might lose virulence and affect testing outcomes.

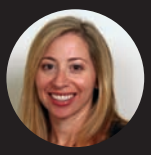
The FDA has now proposed adding *Acanthamoeba* to its testing regimen, accounting for at least two different strains and increasing the challenge level of the free-living amoeba's transformation into a more durable cyst. Additionally, it will focus on the importance of lens/solution interactions, specifically the depletion of the solution biocide (uptake and release) in the presence of a lens, as well as real-world noncompliance issues.

The FDA has also removed the "no-rub" label from all packaging and has increased its public awareness campaign on healthy contact lens wear.[1]

Manufacturers must constantly balance the ability of a solution to kill organisms with potential toxicity to the ocular surface. In the next column, we will discuss the role of toxicology in lens care products. RCCL

1. www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ContactLenses/default.htm

By Elyse L. Chaglasian, OD, and Tammy Than, MS, OD



Topical Delivery to the Posterior Segment—Finally a Reality?

A new report shows promising data. Which hurdles have been overcome, and which remain?

A decade ago, AMD patients were elated to have *any* chance at an intervention that might improve their visual acuity. Intravitreal injection of anti-VEGF was considered a godsend. Nowadays, tedium, expense and risk have dimmed the procedure's halo, but a new study may reveal a promising alternative.

Might doctors one day be able to treat AMD and other posterior segment conditions with an eye drop? Such an advance would provide quantum leaps forward in convenience, safety and perhaps cost, all ideally without sacrificing efficacy.

CAN'T GET THERE FROM HERE

Historically, topical drug delivery has been used to treat anterior segment disease, as most of the instilled drop is lost due to blinking, tear dilution, nasolacrimal drainage and tear turnover.[1] Also, the corneal epithelium, a lipophilic tissue with tight junctions, acts a barrier to reduce ocular penetration by hydrophilic drugs. Rapid systemic absorption also contributes to reduction of ocular absorption; thus, less than 5% of the initial dose is able to reach the aqueous humor, and even less can penetrate through to the posterior chamber.[3,4] Although the conjunctival epithelium is more permeable to larger and more hydrophilic molecules, most clinical drugs are small and lipophilic, thus favoring the corneal pathway and the lipophilic corneal epithelium.[4] The instilled drop slowly diffuses across the corneal epithelium, through the stroma and into the anterior chamber in about 20 to 30 minutes, but with a concentration much lower than upon instillation.

Upon joining the aqueous humor, the drug continues to the iris and ciliary body, and then onto the lens. The crystalline lens is a tightly packed protein matrix that is more resistant than the uvea to drug penetration. While some quantity of a topical drug may flow through the bulbar conjunctiva to the sclera and back to the posterior segment, the amount is clinically insignificant and thus would be ineffective in treating posterior segment diseases.[5]

Various additives can help. *Viscosity enhancers* improve precorneal residence time and bioavailability, or the amount of an administered dose that reaches the systemic circulation unchanged, upon topical drop administration. As a point of reference, a drug administered intravenously has a bioavailability of 100%.[13] *Permeation enhancers*, on the other hand, increase corneal uptake by modifying the corneal integrity to enhance drug bioavailability; however, these additives have been thought to cause local corneal toxicity. *Cyclodextrins*, meanwhile, act as carriers for hydrophobic drug molecules in aqueous solution. They remain in aqueous solution while a hydrophobic drug is absorbed by the biological membrane.[6]

Additionally, *emulsions*, *suspensions* and *ointments* allow for improved solubility, or the dissolution of one solid, liquid or gas into another to form a homogenous system; precorneal contact time; and ocular bioavailability.[6] However, these formulations are associated with side effects such as irritation, redness, inflammation, vision interference and stability issues.[14]

Posterior segment disease requires site-specific drug delivery systems that target the vitreous cavity, RPE and choroid.[7] Other modes of administration for posterior segment delivery include systemic, intravitreal and periocular routes, as well as laser and/or surgical procedures.[4]

While injections can be effective, they must occur frequently to maintain therapeutic effect because of the drug's rapid elimination from the vitreous; this adds to the already considerable cost, inconvenience and host of potential complications (e.g., risk of hemorrhage, infection, retinal detachment, endophthalmitis and cataract).[8] Systemic administration also works, but the high doses necessary for therapeutic effect are often associated with significant side effects. Periocular delivery using subconjunctival or retrobulbar injection is safer and less invasive than intravitreal injection.[4]

DEEP IMPACT

Recently, Ohr Pharmaceutical announced preliminary results from a Phase II trial of topical squalamine to treat wet AMD (the IMPACT study). Squalamine is a small-molecule, anti-angiogenic aminosterol isolated in 1993 from the dogfish shark that works by inhibiting multiple growth factors and pathways responsible for angiogenesis (VEGF, PDGF and bFGF).

The nine-month, double-masked, placebo-controlled study reported data on 62 patients; 29 were treated with an initial ranibizumab injection, then as-needed in combination with squalamine eye drops BID, while 33 were treated with an initial ranibizumab injection, then as-needed and in combination with placebo eye drops BID.

The results suggested a significant treatment breakthrough: 48.3% of patients using the squalamine drops in conjunction with intravitreal ranibizumab gained 15 or more letters, compared to 21.2% using placebo drops. Subjects were also twice as likely to gain over four lines of visual acuity. And, while the results were comparable to previously reported results with anti-VEGF and anti-PDGF intravitreal combinations, the visual benefit reported in the IMPACT study was achieved with far fewer injections (3.8 vs. 12 over 24 weeks). Additionally, the drops were well tolerated, with no adverse events, intraocular pressure rise or cataractous formation.[2]

After administration, this small-molecule drop enters the conjunctiva and anterior sclera, and begins penetrating the corneal epithelium. An mucoadhesive agent is believed to increase corneal residence time so that the drug diffuses slowly over time to the posterior sclera, resulting in delivery of sustained concentrations of squalamine via retardation of loss of the drug through nasolacrimal duct drainage. This also possesses viscosity enhancing properties that may result in a desirable soothing or lubricating effect.

A penetrating enhancing agent allows for greater penetration into the corneal epithelial layers, while a stabilizing agent acts as an antioxidant and can thwart the chemical degradation of the formulation. Buffering agents allow for the drug to be at a near-neutral pH compatible with ocular administration. The tonicity modifier in the formulation produces the appropriate osmolality of the ophthalmic formulation.[15]

Diseases such as AMD can be visually devastating; while today's treatments are more effective than ever, there are still significant downsides. As such, continued research is necessary. Other topically applied agents being investigated for posterior segment therapy include the NSAID nepafenac to inhibit prostaglandin synthesis in the retina and choroid,[16] the kinase inhibitor prodrug TG100801 for neovascularization and retinal edema,[17] the nicotinic antagonist mecamylamine for diabetic macula edema,[18] the tyrosine kinase inhibitor pazopanib for wet AMD[19] and the antisense oligonucleotide aganirsen for retinal neovascularization.[20]

Overall, the promising results of the interim data for squalamine is welcome news to both patients and doctors who are looking for less invasive and more convenient ways to treat posterior retinal diseases such as macular degeneration, diabetic macular edema and venous occlusive disease. RCCL

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LAMELLAR SURGERY: The Bold New Look of Corneal Transplants

By selectively removing only diseased corneal layers, today's surgeons do more with less.

By Aaron Bronner, OD

In 1836, without the aid of modern anesthesia, antiseptic techniques or surgical equipment, Dr. Richard Kissam attempted the first documented corneal transplant on a human, using a pig cornea and two sutures. From these humble beginnings, the field of modern corneal transplantation grew. While keratoplasty has advanced dramatically since that point—benefiting from breakthroughs in eye banking, surgical technique and postoperative immune suppression—the actual surgical procedure performed remained unchanged for more than 150 years following Kissam's attempt.

Penetrating keratoplasty (PK) wore the crown for a century and a half. In the last 20 years, however, new methods of corneal transplantation have reignited interest in the procedure and radically changed the outcomes patients can expect. Work by Gerrit Melles, Mark Terry, Francis Price, Eduardo Arenas Archilla and Mohammed Anwar (among others) has led to the creation of the current lamellar surgical options known by their acronyms DSAEK, DMEK and DALK. These surgeries target only diseased tissue while leaving healthy cornea intact, creating tremendous potential benefits for the patient.

This article will outline the differences between the various surgeries, and their strengths and weaknesses relative to each other.

PENETRATING KERATOPLASTY

Although PK is no longer the sole surgical option in the vast majority of transplants, it is still used in 15% of grafts, so maintaining some awareness of the procedure is important. Further, as the entire central cornea is replaced in this procedure, understanding the benefits and limitations of PK enhances our understanding of lamellar grafts and their strengths and weaknesses.

In PK, the entire corneal thickness is replaced over a 7.5mm to 8.0mm central zone and sutured into place. This procedure is known to have some benefits relative to lamellar surgeries: it's easier to perform, allows for one surgery to be applied across all central corneal pathology and apparently—despite its limitations—may have a better average survival rate than the lamellar alternatives.[1] However, these points are where its value ends.

When compared to lamellar grafts, PK has three fatal flaws: first, as the most antigenic graft, PK is the transplant technique most likely to lead to a rejection episode and also the most likely to have that rejection episode culminate in failure of the graft; second, due to the extensive suturing needed to secure the graft, PK patients have visual recovery that is prolonged and characterized by time-consuming attempts to mitigate high levels of toricity, which can and often does drag out for years; and third, despite best efforts, refractive outcomes are often characterized by high levels of corneal irregularity, often leading to a high dependence on rigid gas permeable contact lenses.

While other real differences persist between PK and the lamellar surgeries, these three issues are what have led to the widespread embracing of lamellar techniques over PK.

DESCEMET'S DOUBLE ADVANTAGE

Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK) are the most recent steps on the surgical continuum that began in the late 1990s with Dr. Melles' posterior

ABOUT THE AUTHOR

Dr. Bronner is a staff optometrist at the Pacific Cataract and Laser Institute of Kennewick, Washington. He has no financial interest in any products or services described in this article.

lamellar keratoplasty (PLK), a treatment for corneal endothelial dysfunction such as Fuch's dystrophy and pseudophakic bullous keratopathy (PBK). Taken as a group, endothelial decompensation historically accounted for nearly 50% of all indications for corneal transplant, making it the most frequently encountered indication for transplant overall and producing a true need for an improved surgery with quicker recovery and less dependence on GP lenses—a niche posterior lamellar transplants have filled.[5]

Both DSAEK and DMEK begin with a limbal or corneal incision, through which the host Descemet's membrane (DM) and endothelium are removed over the central 8mm to 9mm or cornea. A folded or rolled graft (whose exact make-up and behavior is what distinguishes DSAEK from DMEK) is then placed through the same small limbal incision and unfolded within the anterior chamber. Once in position, the graft is then tamponaded with air or high-density gas, depending on the surgeon and the specific surgery performed.

Following the surgery, the patient is observed for a period prior to being sent home with some degree of air still within the anterior chamber, and positioning restrictions are given, with supine posture being recommended over the first few days to a week. This allows residual intracameral air to push the graft into place. Because of the air tamponade, combined with the natural suctioning effect of the endothelial pump, the donor graft will adhere to the host stroma in most cases, allowing for an effective transplantation of endothelium without the use of sutures.

Ignoring the differences between the exact make-up of DSAEK and DMEK grafts for a moment, it can be said that posterior lamellar grafts have some clear benefits over PK. As stated, much of the refractive challenge that comes with a PK owes to the creation of irregular corneal astigmatism by placement of sutures. No matter how skillfully placed, these sutures do not distribute tension evenly across the cornea and can result in marked irregularity of corneal curvature.

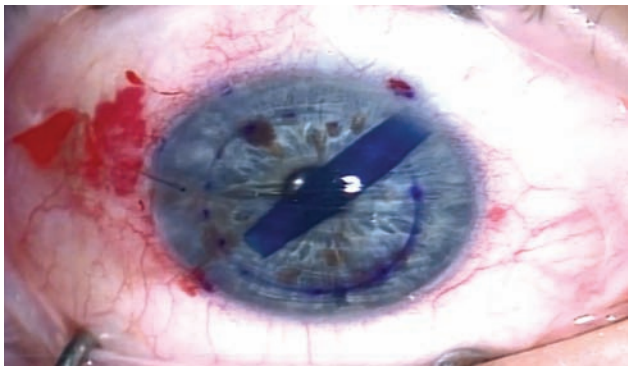

Fig. 1. In this DMEK procedure, a scroll of donor DM tissue within the anterior chamber is stained with trypan blue for visualization.

Posterior grafts avoid this in two ways: first, no sutures are used to secure the graft, helping to minimize corneal irregularity; second, even if the graft isn't completely uniform in its curvature, it affects the posterior corneal curvature, which lessens the effect on overall refraction compared to changes to the anterior curvature as created with PK. The avoidance of irregular astigmatism is particularly valuable within the typical patient population needing keratoplasty for endothelial decompensation. Though no post-transplant patient would choose to depend on GP lenses for vision, such lenses represent a true complication in this generally elderly group where loss of dexterity may be a significant consideration.

The last benefit the lack of sutures generates comes in the form of visual recovery. In PK patients, refraction is not fully stable for several months after suture removal, a step that is often not undertaken until two years after surgery. This leads to final visual stability occuring somewhere around 30 to 40 months postoperatively. In an elderly patient population, waiting up to four years for vision to stabilize is perhaps not the best experience to improve that patient's remaining years of life.

These concepts—GP lens use as a complication and prolonged visual recovery as a waste of a patient's years of quality life—have greatly influenced the perception of and indications for PK compared to posterior transplants for the exact same indication. Previously, when a patient only had PK as an option for visual improvement, doctor and patient would wait until the pathology was causing significant visual debilitation, as the treatment results were often no better than mid-stage disease. In the current era of lamellar transplants, where the twin specters of GP lens use and prolonged visual recovery are no longer issues, doctors are intervening earlier in the disease process to provide patients with more high quality years of life.

The last area where all posterior grafts exhibit some superiority over PK is as antigenic reservoirs. Though both PK and the posterior grafts transplant the permanently persisting antigen of donor endothelium, posterior grafts have a tendency toward preserving the immune privilege of the cornea whereas the sutures, proximity to

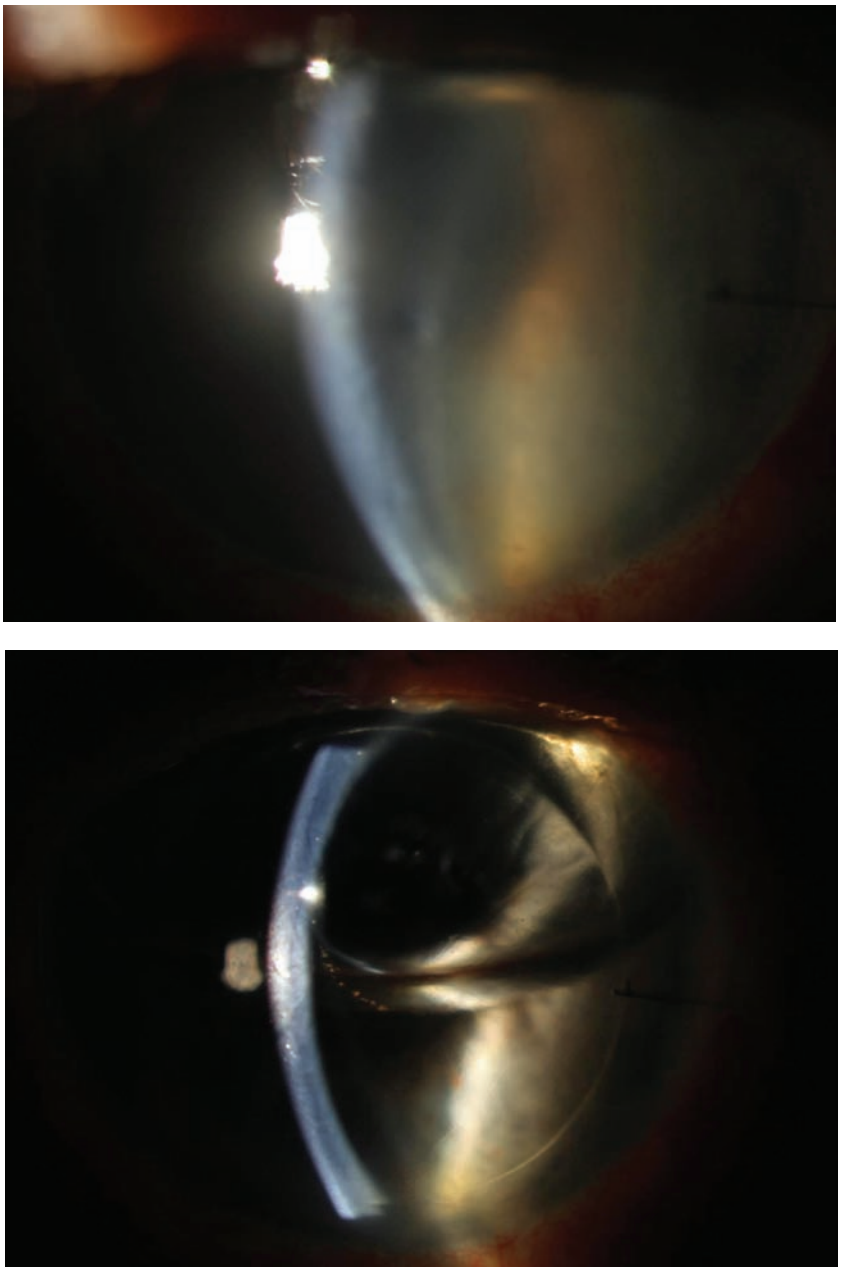

Fig. 2. Top photo: a DSAEK patient with a dislocation of the graft at day one. This is not a rejection episode. Note how edemetous the cornea is, and the graft floating in the AC. Bottom photo: one day after refloating the graft with a larger air bubble, it is in good position and the cornea is already remarkably clear. In cases where repositioning does not work, the graft is said to have failed and a repeat surgery is needed.

deep stromal vascular beds, tendency towards induction of both cornea angiogenesis and lymphangiogeneis and chronic contact lens use with PK creates a pro-inflammatory micro-environment that results in the gradual erosion and loss of corneal immune privilege. This results in a higher rate of rejection episodes overall as well as a higher rate of severe rejection, which leads to failure with PK. This higher risk of rejection then requires a lengthier course of immune suppression with topical corticosteroids, which carry their own host of problems.

As stated earlier, the exact make-up of the graft is what differentiates DSAEK from DMEK. DSAEK grafts are comprised of donor endothelium and DM but also include a portion of posterior stroma, whereas DMEK grafts are made of endothelium and DM only. The stromal component of DSAEK grafts allow for slightly simpler graft preparation as well as intraoperative handling.

It is for these reasons that DSAEK is still the most frequently performed posterior lamellar surgery. Though the posterior stromal component of the graft offers real advantages for the surgeon intraoperatively, it appears to have a negative impact on graft optics, as DMEK patients generally have a quicker recovery and higher visual ceiling compared to a DSAEK equivalent population. In Price's 2009 prospective study on DMEK, patients experienced a three-month BSVA of 20/25, which was equivalent to a one to two Snellen line improvement over the vision achieved by DSAEK grafts at six months.[6]

Further, though both of these grafts contain the exact same recognized level of graft antigen—the endothelium—Price's research indicates that DMEK has a significantly (in fact, paradoxically) lower rate of rejection (1%) than DSAEK (9%) does. These results, if they hold over time, are indicative of some previously unrecognized level of importance that the generally acellular posterior stroma plays in mediating risk of rejection.[7] Despite this significant difference of graft rejection rates between the two posterior

transplants, the rate of graft failure as a result of the rejection episode is significantly lower with DSAEK than with PK and is probably more in line with that of DMEK.[8]

Despite the many virtues of posterior grafts, it is important to recognize that they do have limitations. First and foremost is the increased surgical complexity of these grafts relative to PK. Of the two transplants types, DMEK grafts are more challenging to handle intraoperatively, with tight scrolling of the graft a feature that has kept it from supplanting DSAEK as the most frequently performed poster lamellar transplant.

A second drawback of these grafts is the significantly higher rate of early failure compared to PK. Often inappropriately described as "graft rejection," early failure of a posterior lamellar graft has to do with an insufficient endothelial pump function to create the suctional force necessary to hold the graft in place, allowing it to fall into the anterior chamber (in a PK, it simply manifests as an edematous, non-clearing graft). Most cases of graft dislocation do not represent graft failure and are able to be reattached with injection of more intracameral air; however, grafts that do not adhere after an attempt at repositioning are generally described as having failed.

DALK: THE OPPOSITE APPROACH

Despite being an acronym that looks similar to that of the posterior lamellar transplants, DALK is actually the exact opposite of a DMEK surgery. In deep anterior lamellar keratoplasty, all tissue anterior to DM and endothelium is transplanted and the host endothelium and DM are left behind. Even though only approximately 20µm—the thickness of DM and endothelium—separates a PK from a DALK, it has some important advantages over PK all having to do with its ability to maintain host endothelium.

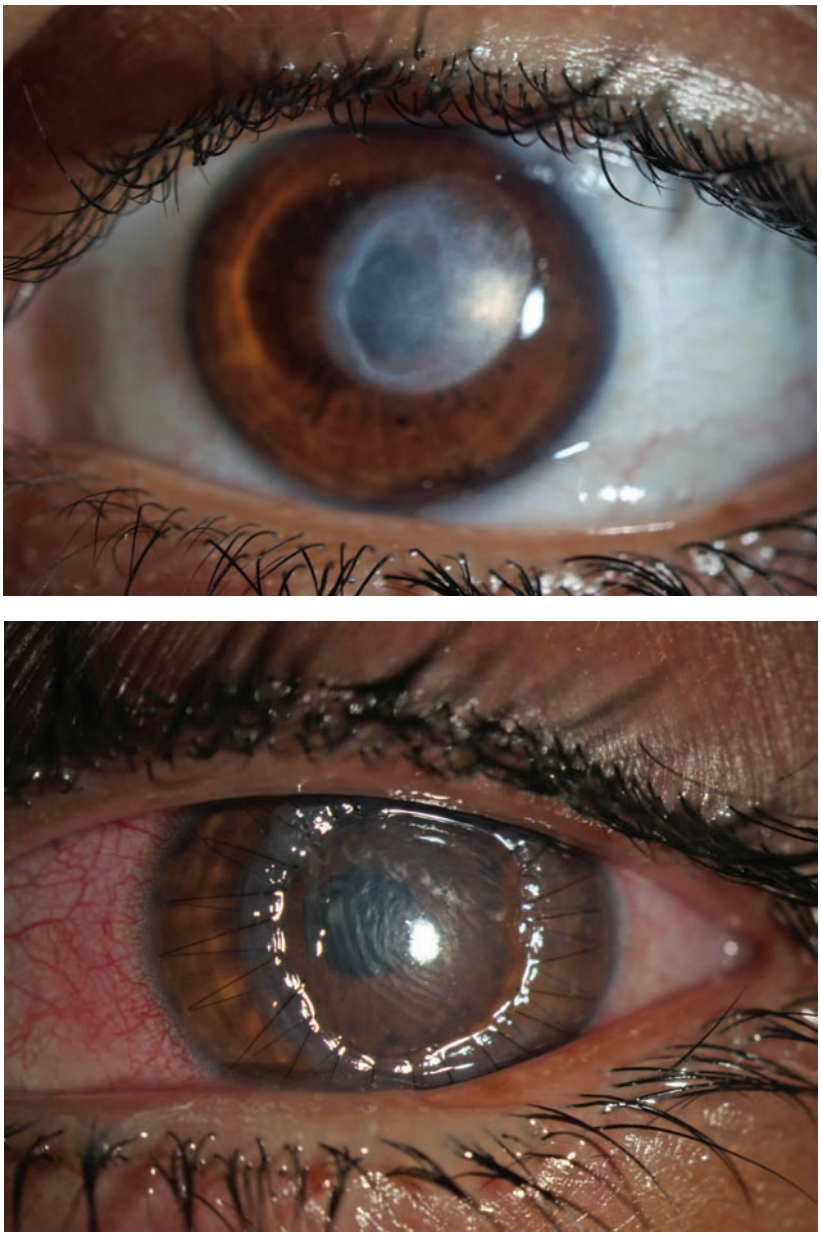

Fig. 3. This patient presented after treatment for a severe infectious ulcer (top photo). Because the resultant scar was too deep for PTK, DALK was elected. The bottom photo shows the typical appearance at one day post-op, with no epithelium present and mild stromal edema. Secured with a running suture, clinically this is near impossible to differentiate from a PK.

Technically difficult and time-consuming, DALK requires manual dissection of host stroma paired with the injection of intracorneal air to pare down to the host DM. Due to potential for perforation of Descemet's membrane, which occurs in as many as 32% of all attempted

WHY'S THE ENDOTHELIUM SO IMPORTANT IN CORNEAL GRAFTING?

When considering corneal transplantation, there is no doubt the endothelium is the most crucial layer, even when it remains intact (as with a DALK). There are three reasons why.

First, of all tissue transplanted, only nucleated cells carry the necessary antigens to induce a rejection episode by the host immune system. Of the transplanted nucleated cells, only endothelial cells are non-miotic, and as such any damage they incur is permanently resident in the cornea; correspondingly, once they are transplanted, they persist indefinitely as a source of graft antigen. Transplanted epithelium and keratocytes, on the other hand, are replaced by host cells (as their stem cell regions fall outside the margins of the graft) at some point within the postoperative period—this occurs rapidly with epithelium, and slowly for keratocytes. Therefore, donor-derived corneal endothelium is the only possible permanent target of rejection.

Second, once again owing to their non-miotic status, damage done to donor endothelium by an immunologic attack—when sufficient—can result in failure of the graft due to endothelial decompensation, making endothelial rejection the only type of rejection that can typically generate graft failure.

Lastly, transplanted endothelial cell density (ECD) is reduced dramatically as a result of surgery, to the point that all transplants containing endothelium have a 35% to 45% reduction in ECD within the first year postoperatively. This likely correlates with an abbreviated life expectancy for grafts that contain endothelium, a feature that has been shown with PK and will likely bear out with posterior lamellar grafts as well.

DALKs during this step, 18% all of DALK cases are converted to PK intraoperatively. Once the host stroma is removed, the donor tissue, which carries all tissue anterior to DM, is sutured into place. Because of the extensive suturing and clear optical interface at DM, in clinic it can be impossible to differentiate a DALK from a PK.

Even though DALK is a tedious surgery with high risk of intraoperative failure and patients experience the same slow visual recovery as PK (due to sutures), it has become the transplant of choice for all anterior pathology such as keratoectasias, deep scars and stromal dystrophies due to the immunologic benefits of maintaining the host endothelium.

Because the endothelium is not transplanted, a DALK graft has two dramatic advantages over a PK. First, non-transplanted endothelium loses cell density very gradually, whereas procedures that transplant the endothelium result in an accelerated loss of endothelium function. Because of this, DALK grafts are expected to persevere indefinitely without regrafting—a dramatic improvement over PK grafts, which have a finite uncomplicated lifespan of roughly 20 years. Within the patient population of keratoectasias, patients who need a regraft every 20 years may need three transplants in their lifetime. Second, there is a dramatic reduction in the risk of graft rejection with a near-absent risk of failure as a result of rejection. Ancillary benefits are then achieved by a lessened dependence on corticosteroids, which produces lower rates of steroid-induced glaucoma (a common source of vision loss with PKs), infection and cataract development.[9]

After well over a century of penetrating keratoplasty, the last two decades have moved eye care out of the era of full-thickness keratoplasty and into the era of lamellar keratoplasty. Never before have patients and doctors had the option to select a surgery that will treat only diseased tissue and spare healthy structures, resulting in a quicker recovery with less potential for complication. Understanding the options and their limitations will allow us to help patients select the most appropriate surgery for their pathology, as well as follow up with them appropriately. RCCL

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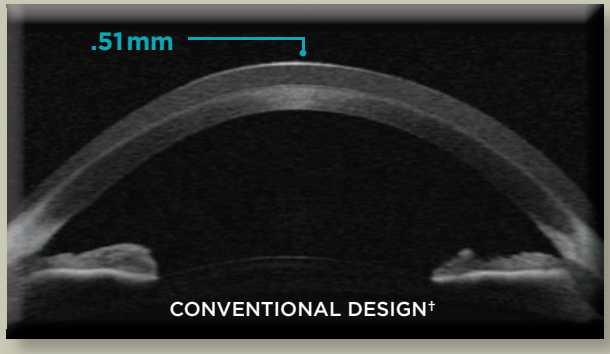
Two approaches to treating irregular corneas with custom soft lenses.

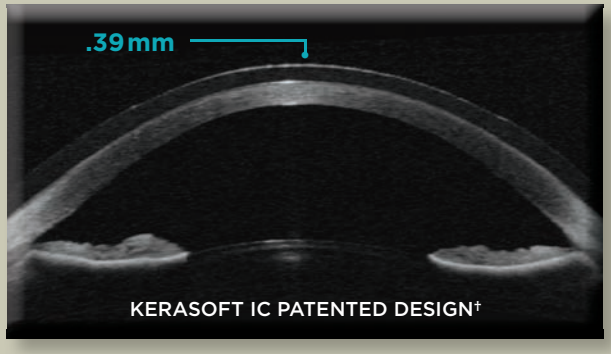
In its time

Thickness of material



In its prime

Anterior aspheric optics



† Images represent horizontal scan of -3.00D lenses. KeraSoft® IC uses prism ballasting.

KeraSoft® IC. The prime time approach.

When treating irregular corneas with a soft lens, there was a time when "thickness of material" was thought to be the best approach. Today, there is KeraSoft® IC. Its patented design "drapes" over the cornea to correct the vision rather than simply "mask" the irregularity. This enables KeraSoft® IC to have a thinner optical center than in traditional designs, while still providing excellent visual acuity – a significant factor to consider when choosing a lens that meets your patient's needs. And for comfort, KeraSoft® IC is made of a quarterly replacement silicone hydrogel*.

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KERATOCONUS SURGERY:

By Martin L. Fox, MD, FACS

Keratoconus is best described as a family of ectatic corneal dystrophies characterized by loss of collagen, corneal thinning and a weakening of structural integrity. With aggressive progression, these changes result in the alteration of corneal morphology that can lead to the loss of best-corrected acuity and eventual visual disability.

Traditionally, practitioners managing visually significant keratoconus have been somewhat limited in therapeutic options. Primary visual rehabilitation methods consist of progressive contact lens options and modifications such as custom toric GP lenses, hybrids, "piggy-back" fits and scleral lenses. However, with potential contact lens intolerance and recurring keratitis due to surface allergy and dry eye, patients can develop anterior corneal scarring and diminished acuity, prompting surgical referral for keratoplasty.

Now, recent developments in surgical management options offer fresh hope for the more severely-affected keratoconus population, while new diagnostic technologies can now uncover the earliest of corneal ectasia alterations. Such cutting-edge detection can allow doctors to refer young patients for collagen crosslinking therapy (CXL) that can arrest the ectatic process, thus saving those affected from a lifetime of visual disability. We have reached a point where the real possibility of early diagnosis and CXL management can offer the hope of halting the advance of this disease.

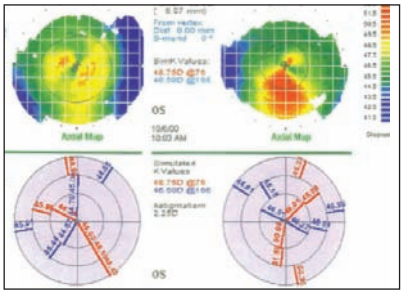


Figure 1. Asymmetric bow-tie pattern with skewed radial axis.

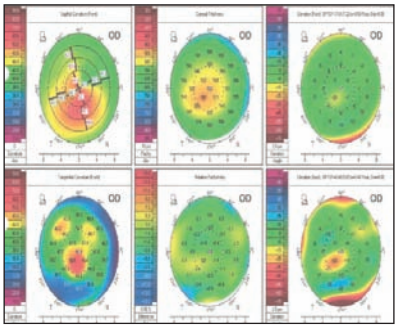


Figure 2. Pentacam tomography showing early keratoconus.

EARLY DIAGNOSIS IS KEY

Patients with early changes suggestive of keratoconus often present for routine evaluation. Irregular retinoscopy reflex and red reflex, progressive "against-the-rule" astigmatism and loss of best spectacle-corrected visual acuity are all red flags that should alert one to the possibility of nascent corneal ectasia. Corneal topography revealing inferior corneal steepening or irregular non-orthogonal bow-tie astigmatism patterns and thin corneal pachymetry readings of 500µm or less is also essential in the diagnostic process as well (*Figure 1*).

It is crucial that such patients be referred to a center where testing with elevation tomography (*Figure 2*) can be performed, as it can often reveal subtle elevation changes on the posterior cornea that might not otherwise be apparent. Such changes can be an early harbinger of the ectatic process; clinical suspicion in the examination room is key.

COLLAGEN CROSSLINKING

The seminal work of Theo Seiler demonstrated that when the cornea was exposed to a narrow spectrum of UVA light after saturation with 0.1% riboflavin (vitamin B2), a process of photoactivation could produce a chemical reaction that increased covalent crosslinking bonds between tri-helical collagen strands and lamellae.[1] This crosslinking phenomenon reportedly resulted in a 300% increase in corneal stiffness.

Long-term data on patients so treated in the early investigation of CXL showed that 81% to 100% displayed no further progress in the ectasia process.[2-4] At our clinic, a three-year experience of treating patients using the epithelium-off approach has thus far documented a complete halt in progression in young patients presenting in the early stages of aggressive ectasia.

ABOUT THE AUTHOR

Dr. Fox is the Medical Director of the Corneal and Refractive Surgery Practice of New York and Clarity Refractive Services of West Orange, NJ. He has over 30 years of experience in refractive surgery as a surgeon and investigator. He can be reached at 917-207-3147 or by email at foxmd@laserfox.com.

The Shape of Things to Come

New diagnostic and operative techniques may soon benefit practitioners and patients.

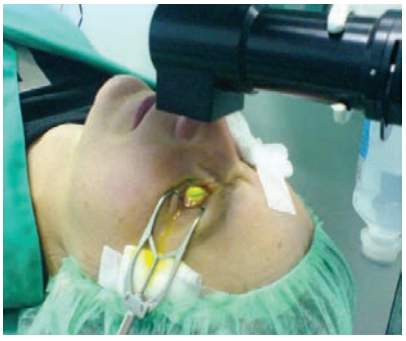


Figure 3. A patient undergoing epi-off collagen crosslinking.

Our patients are treated in our refractive surgery suite, where 7mm of central corneal epithelium is removed after exposure to diluted alcohol. Riboflavin 0.1% drops are then instilled every two minutes for 15 applications. Prior to UVA treatment, corneal thickness is checked for a minimum of 400µm to assure endothelial safety. A bandage contact lens is placed on the eye for five days following treatment, and drops consisting of prednisolone acetate 1% and a fourth-generation fluoroquinolone are advised.

Currently, a debate exists as to whether "epi-on" CXL is as effective as the classic "epi-off" approach that we use in our clinic. Our feeling is that complete saturation of corneal stroma with riboflavin and the exposure of the cornea to oxygen is extremely essential to a safe crosslinking process.

Post-op management is similar to that of PRK patients. The treatments have been well tolerated and uncomplicated; however, pain, photophobia, poor healing response and infection have been reported as possible side effects.[4]

It is important to note that while crosslinking has been reported to improve BCVA by creating corneal flattening and reducing irregular astigmatism, the treatment is primarily aimed at halting disease progression, and patients should be so educated.[5] Those with advanced disease are often poor candidates for crosslinking alone; once the disease has fully expressed itself, other options must be considered in conjunction with CXL for ideal results. Currently, CXL awaits final FDA approval in the US.

INTRASTROMAL RINGS

The Intacs technology was the brainchild of Oklahoma optometrist Gene Reynolds, who developed it as a treatment for low myopia in 1978. Placement of these semicircular polymethylmethacrylate rings of varying thickness in the cornea was found to flatten corneal radius of curvature. However, the advent of excimer laser in the treatment of myopic refractive errors displaced the technique until 2000, when French ophthalmic surgeon Joseph Colin recognized that selective ring placement could also have a beneficial effect in regularizing corneal morphology when applied to corneas with ectatic dystrophies.[6]

In a prospective study by Kartakis and associates in 2003, 33 eyes of 26 keratoconus patients received two 0.45mm segments.[7] The average follow-up was 11.3 months (ranging from one month to two years) and the mean uncorrected acuity improved from 20/160 to around 20/50. Two eyes lost a line of uncorrected vision, three stayed the same and 28 experienced gains of one to 10 lines. The mean BCVA improved from around 20/40 to a little better than 20/32. Four eyes lost one to two lines of vision, while 25 eyes gained one to six lines. Intacs surgery for keratoconus was approved by the FDA in 2004.

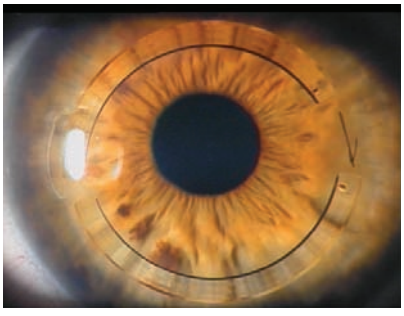


Figure 4. Intacs rings placed in a keratoconic patient.

Modern surgical approaches in the use of Intacs rings have now evolved to the point where they have become a viable option in our approach to rehabilitating patients with visually significant keratoconus. When properly performed using femtosecond laser technology, patients with symptomatic keratoconus can obtain better uncorrected "walking around" vision, improved spectacle-corrected visual acuity and better contact lens tolerance.

MATCHING PATIENTS AND PROCEDURES

Typically, when I evaluate patients referred for keratoconus, I approach each case from two distinct standpoints: risk of progression and degree of visual impairment. Those early in the disease course are best

INTACS PERFORMANCE IN PRACTICE

Case 1: Asymmetric Oval Type

A 43-year-old male presents with asymmetric keratoconus. A surgical procedure implanted a single ring 0.45mm at axis 65 with simultaneous collagen crosslinking.

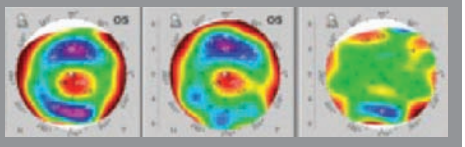


Figure 5. Asymmetric difference map.

	Pre-op	Six Months Post-op
Keratometry	54.5/57.7x 68	47.9/53.3 x 90
UCVA	20/400	20/50
BSCA	Plano -6.00x68, 20/100	-1.00-2.50 x 80- 20/25

Case 2: Symmetric Round Type

A 26-year-old female presented with symmetric keratoconus and contact lens intolerance. The surgeon used symmetrical 0.45mm rings with collagen crosslinking.

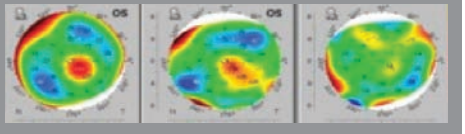


Figure 6. Symmetric difference map.

	Pre-op	Three Months Post-op
Keratometry	50.1/54.1x 59	49.2/52.3x 60
UCVA	Count Fingers	20/400
BSCA	-6.25-3.25x 180, 20/50	-4.25-4.25x 125, 20/30
Toric SCL Acuity		20/25

addressed with CXL alone, but we advise those with significant visual function issues to consider Intacs ring placement in concert with CXL as the two have a synergistic effect in surgical outcomes.

A clinical evaluation of a keratoconus referral consists of a complete examination, including Pentacam tomography to better delineate the pattern of ectasia and corneal thinning. Evaluation of the corneal red reflex with a direct ophthalmoscope allows for the characterization of ectasia patterns as central symmetric (round type) or asymmetric (oval type). Such findings are essential in planning the appropriate custom surgical approach. Symmetrical surgery consisting of insertion of two rings on the steep meridian with round central cases and asymmetric (varying thickness) or single ring placement is typically used in the approach to oval sagging pathology.

In our refractive surgery suite, the Intralase femtosecond laser is used to create ring channels at a depth of 75% of the thinnest corneal pachymetry at a radius of 7mm around the visual axis. The entrance incision is placed at the steepest corneal axis as determined by Pentacam tomography and manual placido ring topography. Following ring placement, CXL is added in the manner outlined above to enhance the flattening effect of ring placement. Patients can expect to experience an evolution of visual improvement over a period of two to three months.

In general, patients with symmetrical findings and corneas with mean keratometry of less than 58 diopters can expect good response when treated with conventional Intacs rings.[7,8] Those with corneas steeper than 58D do not respond as well, but remain viable candidates if expectations are limited to achieving better contact lens tolerance.

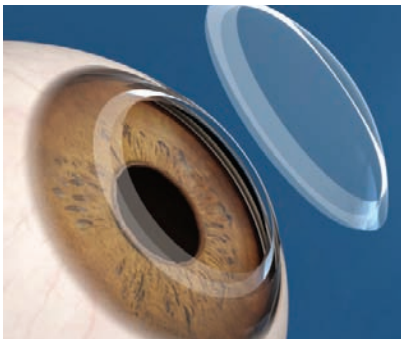
These patients may benefit from specialty Intacs devices manufactured with an SK modification, which are placed at a 6mm optical zone and have demonstrated a significant improvement in patient response. Unfortunately, they are currently unavailable and awaiting FDA approval.

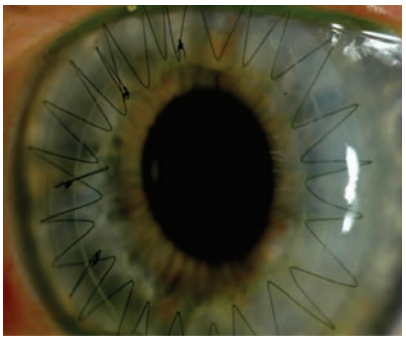
In our clinic, individuals with sagging oval asymmetric pathology have been shown to do well with single or asymmetric ring placement with mean keratometry readings of up to 60 diopters. Individuals with significant scarring are not good candidates for Intacs surgery except in rare cases where, in conjunction with CXL, goals limited to corneal stabilization and contact lens modification are anticipated. For those patients outside of Intacs treatment range, consider femtosecond laser-assisted keratoplasty.

FEMTOSECOND LASER-ASSISTED KERATOPLASTY

Perhaps the greatest advance in corneal transplant surgery has been the addition of femtosecond laser technology. It completely altered the landscape of laser vision correction by allowing surgeons to create predictable LASIK flaps that could be customized to the architecture of each eye. The resulting planar flaps, when used in combination with custom excimer laser ablations, has allowed for superior safety, stability and visual outcomes.

Prior to the advent of laser-assisted keratoplasty, patients having transplant surgery with standard mechanical trephine or mechanical punch transplant surgery could





Figures 7 & 8. Zig-zag pattern Intralase-enabled keratoplasty.

expect a lengthy period of visual rehabilitation upwards of one year. Outcomes notoriously included high levels of irregular astigmatism and wound instability. With femto technology, however, these concerns are no longer viable and the once-dreaded keratoplasty procedure has improved in both recovery speed and outcome predictability.

In femtosecond laser keratoplasty, the corneal surgeon can either calculate a unique pattern of corneal cuts or work off a set group of pre-calculated templates that best fit the patient. Participating eye banks will make use of the same corneal cut parameters to prepare donor tissue. In the operating room, recipient pathology is removed and the custom corneal replacement sutured in place. The precise match of donor and recipient allows for a number of very significant improvements in patient rehabilitation and outcomes. Furthermore, we have found that when a zigzag wound profile is used, increased wound healing interface creates a distinct improvement in wound stability (*Figures 7 and 8*).

Currently, a series of 14 consecutive keratoconus cases performed over a one-year period with the Intralase femto laser zigzag patterning is under study in our clinic. We have thus far documented visual rehabilitation during a three- to six-month follow-up period. The series consisted of patients ranging in age from 22 to 62 with BSCVA range of CF to 20/100. Three-month post-op data revealed 100% of cases with spectacle-corrected visual acuity of 20/40 or better, with 64% achieving correctable vision of 20/25 or better. In Intralase-enabled keratoplasty (IEK), precise matching of complex donor and recipient tissue planes has allowed for accelerated healing, enabling the removal of sutures as early as six weeks post-op with more than 75% of patients manifesting very acceptable levels of regular astigmatism (2.5D or less.)[9]

Femto laser technology can also allow for safe astigmatism "touch-ups" for patients with higher levels of postoperative astigmatism. Using the anterior side-cut setting of the Intralase, we can place very safe, accurate astigmatic keratotomy arcuate incisions inside of the graft/host interface to address any astigmatism concerns.[10]

SUMMARY

Surgical management of keratoconus has clearly reached a point in time where we can offer new hope to this population of patients. To best share these developments, it is incumbent upon all providers of primary eye care to be well acquainted with the options now available.

Of greatest importance is early diagnosis, as patients who present at early stages of the ectasia process require referral and intervention. Primary eye care providers need to be aware of the warning signs of early or progressive keratoconus and be prepared to participate in comanagement.

Timely CXL has been demonstrated itself to provide the opportunity to halt disease progression in young patients who might otherwise be passed over. For those KCN patients unable to tolerate contact lens correction, precise placement of Intacs intrastromal rings can reshape corneal morphology, allowing for improvement in BCVA as well as contact lens tolerance. Patients presenting with advanced disease should be considered for laser-assisted keratoplasty, which offers the prospect of rapid recovery of quality vision and corneal stability. RCCL

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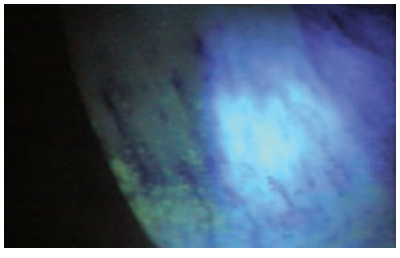
Dry Eye: Can You Tackle These Tough Cases?

Perhaps because it's both commonplace and chronic, dry eye presents a seemingly never-ending series of challenges: the "easy" cases are hard, and the hard cases can be maddening. Some patients who should respond to routine therapy simply don't, while others have symptoms far out of proportion with their signs and general medical history. And even effective therapies can be stymied by noncompliance.

While much is known about ocular surface disease, it still remains a complex condition with many causes and potential treatment options. Often, the approach to management involves as much art as science. For this reason, we asked several dry eye experts to weigh in on how they would diagnose and treat the following recalcitrant cases.

CASE 1: LONG-SUFFERING SJÖGREN'S PATIENT



A 67-year-old female with a five-year history of Sjögren's syndrome presented complaining of extreme discomfort and light sensitivity. Visits to numerous eye care practitioners, including a cornea specialty group, didn't provide significant relief.

In addition to over-the-counter drops for dry eye, she was currently using a topical fluoroquinolone and a formulated vancomycin drop for a lingering corneal infection, as well as Restasis (Allergan) to increase tear production. However, nothing seemed to be providing relief from severe irritation and photophobia symptoms, which had become debilitating.

Her noninvasive tear film break-up time was three seconds, with significant areas of corneal staining, suggesting tear instability. In addition, meibography revealed significant gland truncation and some gland loss, while diagnostic meibomian gland expression showed nearly all glands blocked, with minimal expression of thick, opaque meibum. The patient's tear prism was noted as barely present; interferometry confirmed a deficient lipid layer.

A slit-lamp exam revealed a dense band of staining with areas of indolent corneal ulceration and haze across the right cornea below the midline. The left eye had no ulceration but did exhibit dense staining in a similar inferior-midline pattern. Careful examination of lid/globe apposition showed a significant gap on closure, while testing of Bell's phenomenon showed that it was essentially absent in both eyes.

What's the best course of treatment for this patient?

Dr. Karpecki: The ocular surface exposure from poor eyelid apposition is perhaps the number one reason the patient is having so many problems, Dr. Karpecki notes. Overnight bland ointments and sleep shields would likely help with the nocturnal lagophthalmos.

To address the existing issues, the first step is to heal the corneal ulcer and protect the ocular surface integrity, Dr. Karpecki says. Given the length of time the patient used vancomycin without improvement, the issue may be toxic keratitis, a Mooren's ulcer or an ulcer related to a systemic disease such as a peripheral ulcerative keratitis (PUK) from rheumatoid arthritis or another autoimmune condition associated with Sjögren's syndrome.

Ultimately, determining the degree of pain would help with the diagnosis. "I'd contact her rheumatologist and ensure that the specialist assesses the systemic disease, as a PUK could be a systemic manifestation," Dr. Karpecki explains.

Using an oral secretagogue such as Evoxac (Daiichi Sankyo) 30mg BID to TID for the dry mouth that is likely present could also help the dry eyes, Dr. Karpecki suggests, adding that he would continue with an antibiotic but discontinue the vancomycin due to its potential toxicity and amount of time used.

Next, Dr. Karpecki would address the need for increased lubrication of the ocular surface, then apply an amniotic membrane such as Prokera (Bio-Tissue) if the ulcer or persistent epithelial defect does not respond.

Further testing such as tear osmolarity could be illuminating as well. "I would be at a loss for how to best treat this patient without knowing her osmolarity readings, in addition to symptoms, meibomian gland expression and ocular surface staining," Dr. Karpecki notes. Meibography and lid closure assessment or blink would also be valuable findings.

Experts walk us through their approach to refractory disease. With multiple factors to address, opinions may differ. What's yours?

By Jane Cole, Contributing Editor, and Aliza Martin, Associate Editor

Most Sjögren's patients have osmolarity readings above 330mOsmol/L; a patient on Restasis for a substantial period of time, however, may show significant improvement, Dr. Karpecki says. "Given her continued symptoms, I'd predict the reading to be around 315 to 320—that is, improved on Restasis—but given the severity of the disease, additional therapies may be required." Blocked meibomian glands in a Sjögren's patient indicate concurrent and long-standing disease, which is typical, "but the key is the lack of apposition of the eyelids," he says. "This finding over time will cause significant obstruction, dysfunction, dropout of the meibomian glands and exposure keratopathy."

Assuming the osmolarity tests high, Dr. Karpecki suggests changing her artificial tears to a drop more likely to lower osmolarity, such as Blink (Abbott Medical Optics), TheraTears (Advanced Vision Research), FreshKote (Focus Laboratories) or Retaine (Ocusoft). Preservative-free versions should be used if the reading is extremely high (i.e., >330 in at least one eye). If the osmolarity reading were slightly elevated to normal on Restasis (i.e., <315), he would recommend using a lipid-based or lipid-enhanced artificial tear such as Refresh Optive Advanced, Systane Balance, Soothe XP (Bausch + Lomb) or Retaine MGD, and continuing the Restasis.

Additionally, because this level of obstruction and meibomian gland loss requires aggressive therapy, Dr. Karpecki would prescribe 50mg BID doxycycline for one to three months, then taper the doxy and begin a nutritional supplement such as HydroEye (ScienceBased Health) for long-term use.

Dr. Karpecki would also recommend a warm compress (e.g., Bruder Eye Hydrating Compress) and would place the patient on a topical anti-inflammatory/antibiotic for approximately two weeks, preferably a preservative-free option in light of the keratopathy present, and would continue the Restasis BID. If significant improvement is not noted over the next one to three months, an in-office gland expression therapy like LipiFlow could also be considered.

"Once the disease is controlled from all of these steps," he said, "I'd have her continue the Restasis, HydroEye, the appropriate artificial tear and the Bruder Eye Hydrating Compress long-term, in addition to good systemic control of the autoimmune disease."

Dr. Hauswirth: While agreeing with Dr. Karpecki's initiative to tackle the corneal ulcer first, Dr. Hauswirth suggests starting treatment of the meibomian gland problem with LipiFlow or manual therapeutic gland expression in addition to oral doxycycline.

"As this is a Sjögren's patient, we would expect that her lacrimal function is decreased, but any amount of aqueous tear production she has would be better served with improved meibomian function and a thicker meibum layer," he explains.

In addition, he suggests adding autologous serum drops to allow growth factors and other beneficial proteins for the epithelium, and anti-inflammatories. Punctal occlusion once the inflammatory markers are reduced would also be beneficial.

Dr. Aldridge: "If this is a true infection and not a sterile ulcer," Dr. Aldridge cautions, "Restasis is contraindicated and needs to be stopped until the infection is cleared."

The patient is also likely suffering from aqueous deficiency—common in those with Sjögren's—and evaporative deficiency as evidenced in the meibomian glands. In addition, "to complicate it more, there seems to be an exposure keratitis being created from the lack of lid closure," Dr. Aldridge added.

The antibiotics unfortunately must be continued despite appearing abrasive on the ocular surface. Dr. Aldridge would

CONTRIBUTORS

***Chuck H. Aldridge, OD**, is head of Aldridge Eye Institute in North Carolina.*

***Mile Brujic, OD**, practices full-scope optometry with special interest in contact lenses, anterior segment disease management and glaucoma as part of the Premier Vision Group in Ohio.*

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***Paul M. Karpecki, OD**, heads the ocular surface disease clinic and is director of clinical research at the Koffler Vision Group in Lexington, Ky.*

***Joseph P. Schaeffer, OD**, the Clinical Editor of Review of Cornea & Contact Lenses, practices at Northeastern Eye Associates in Pennsylvania.*

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***Scheffer C. G. Tseng, MD**, serves as the medical director of the Ocular Surface Center in Miami, Fla.*

consider adding an antibiotic ointment to help with lubrication. Once the infection clears, punctal plugs to increase tear volume could be inserted. The patient should then resume using Restasis.

After a few weeks, Dr. Aldridge would monitor corneal staining during a follow-up examination. If signs and symptoms don't improve, he'd consider fitting a mini-scleral contact lens to put a reservoir of fluid against the corneal surface for most of the waking hours.

Dr. Tseng: In contrast with the others, Dr. Tseng suggests addressing the corneal infection using punctal occlusion with cautery if there is no reflex tearing. Following the procedure, He'd use a corneal bandage such as Prokera Slim to help the corneal epithelium heal. Autologous serum drops can be used later to maintain ocular surface health.

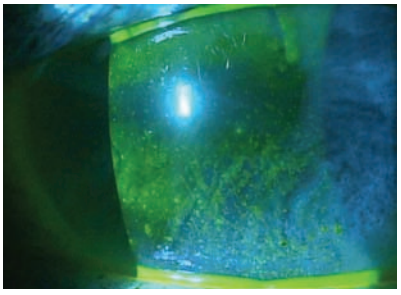
Regarding the meibomian gland dysfunction, Dr. Tseng suggests looking into alternate causes, such as Demodex infestation. If epilated eyelashes and cylindrical dandruff are noted, he says, the problem can be treated using a preservative-free facial cleanser like Cliradex (Bio-Tissue).

Dr. Epstein: Dr. Epstein, who submitted this case, prescribed doxycycline 50mg BID and recommended the patient begin using HydroEye, a nutritional supplement. He initially treated the exposure using a bland ointment at nighttime before switching to the EyeEco Quartz silicon sleep shield. The patient's use of topical vancomycin was discontinued and the generic fluoroquinolone was switched to Vigamox (Alcon) for 10 days to minimize toxicity, then suspended after resolution of the ulceration was noted. Use of Restasis was continued and the patient was told to keep well hydrated.

The patient's discomfort and photophobia improved only slightly following adoption of this regimen, so bandage lenses were fitted successfully with excellent results following discussion of risks and benefits.

The patient currently uses warm moist heat goggles (Tranquileyes by EyeEco) nightly, and meibomian gland expression using the LipiFlow system is planned for the future. The patient continues to do well on the current regimen.

CASE 2: ALTERNATIVES FOR NONCOMPLIANCE



A 66-year-old diabetic male presented with a diagnosis of dry eye. He was being treated with Systane Ultra, which he reported using "about once a day." His dry eye severity was tested with InflammaDry (RPS), an in-office inflammatory marker test, resulting in a "strong positive" reading. The patient admitted he had problems with compliance and remembering to "use the drops." Prescription options were discussed and the patient expressed an interest in using nonprescription options, if possible.

How would you treat this patient?

Dr. Schaeffer: The first step is to perform a complete ocular surface evaluation, says Dr. Schaeffer. Depending on slit-lamp findings and dry eye severity, treatment options include medications such as Lotemax (Bausch + Lomb) gel BID; Restasis BID or TID; lipid-based artificial tears such as Systane Balance, ointment or gels QHS; Lacrisert; meibomian gland treatment options such as expression, hot compresses, doxycycline, antibiotic/steroid drops or LipiFlow; punctal plugs and omega-3 supplementation.

Dr. Karpecki: Consider additional testing—e.g., osmolarity, meibomian gland expression (and meibography, if available), and, fluorescein dye—to quickly gauge the staining, tear meniscus height, clearance and tear film breakup time, suggests Dr. Karpecki. "Without those tests, it is difficult to determine the most appropriate treatment especially given the fact that the patient expressed an interest in non-prescription products," he explained.

If osmolarity was found to be elevated (i.e. above 320mOsmol/L), artificial tears like TheraTears, Blink, Retaine and FreshKote have a greater propensity to lower osmolarity are more likely to achieve quicker results, he says. "My assumption, given the specifics of this case, is this patient's osmolarity was below 320 and the meibomian glands did not show significant disease," Dr. Karpecki says. "In that case, a tear like Systane Ultra would work well."

Due to the level of inflammation noted, treatment options include ocular nutrition, oral doxycycline, Restasis and corticosteroids. "Given the patient's desire to start with nonprescription options," he says, "I agree with the nutritional treatment approach. One could then step up therapy if resolution was not achieved."

Finally, the patient's diabetes should be monitored, as dry eye can also be a manifestation of poorly controlled disease. For this, a letter to the endocrinologist or PCP would be prudent, he says.

Dr. Hauswirth: Because "compliance and cost are both issues that become more challenging in less symptomatic patients," Dr. Hauswirth would first attempt to address compliance through patient counseling, focusing on the patient's risk of progression in the presence of diabetes and a positive MMP-9 marker. "He needs to know that artificial tears in this case is not the same thing as treating it medically."

Dr. Hauswirth advises using Lotemax gel TID for one month to address the ocular inflammation, as well as Restasis BID. "This patient may well have reduced corneal sensation due to partial neurotrophia. The improvement in the ocular surface and InflammaDry markers may be initially offset by the patient 'noticing' his eyes more, which is a good sign—it means we may be regenerating some of the corneal nerves," he says. In any case, however, "his age, systemic condition and high risk of progression will make this a longer treatment regimen."

Dr. Brujic: As the doctor who treated this patient, Dr. Brujic prescribed Systane Ultra TID, EZ tears (EyePromise, ZeaVision), a nutrition supplement containing omegas 3 and 6, vitamins A, D3 and E, and other components to enhance the tear film.

During a three-month follow up, the patient reported poor compliance with artificial tears but good compliance with ocular nutrition. InflammaDry testing showed a "weak positive" result, suggesting decreased inflammation. Ocular surface findings improved with minimal staining and an improved TBUT. Dr. Brujic continues to treat the patient with ocular nutrition and Systane Ultra.

CASE 3: THE GREAT MASQUERADER

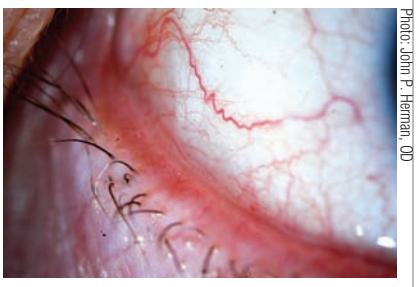


Photo: John P. Herman, OD

A 78-year-old female presented complaining of significant ocular irritation, redness of the conjunctiva and epiphora in both eyes. She reported her last eye care provider diagnosed her with an aqueous deficient dry eye with a secondary reflex tearing. She was placed on a regimen of artificial tears and Restasis 0.05% BID, warm compresses and lid hygiene without improvement. Her conjunctiva was significant for redundant folds inferiorly.

Dr. Tseng: "The clinical history of this case suggests the patient has both aqueous-deficient dry eye and conjunctivochalasis, while being refractory to conventional medical treatment," Dr. Tseng says.

Because conjunctivochalasis is a mechanical problem that eliminates the tear meniscus and the tear reservoir in the fornix, one possible solution could be to repair both using cryopreserved amniotic membrane in a surgery known as the reservoir restoration procedure. Following the procedure, if symptoms persist, Dr. Tseng suggests punctal occlusion.

Dr. Hauswirth: Application of a corticosteroid such as Lotemax gel BID or compounded Pred-Healon (prednisolone sulfate 0.25% in hyaluronic acid) two-to-three-times daily over a month's time may alleviate some inflammation and other symptoms that result from conjunctivochalasis, Dr. Hauswirth says. Topical antihistamines or NSAIDs may also be used, but he cautions they are not as dependable in this scenario.

In the longer term, Dr. Hauswirth recommends oil-based non-preserved artificial tears, such as Refresh Optive Advanced, in combination with Restasis. "Appropriate education is critical in this scenario for the patient to understand that anti-inflammatories may only help a small amount as far as symptoms go, but may slow down the progression of the disorder," he says.

To ultimately correct the pathology in highly symptomatic patients, however, Dr. Hauswirth advocates a surgical consultation with excision of redundant conjunctiva, which he says has been shown to help reduce inflammatory markers and restore a more normal tear reservoir.

Dr. Schaeffer: "Conjunctivochalasis is a very undiagnosed condition that leads to many ocular complications," says Dr. Schaeffer. If the folds are blocking the puncta or the meibomian glands, or just irritating the eye, he agrees surgical correction will be needed. In this case, the conjunctiva folds are most likely causing the epiphora.

Because this patient also has issues with her canalicular system, Dr. Schaeffer suggests a lacrimal system irrigation to open or measure the patency of the tear drainage duct. He also would consider other options to improve tear volume.

(Continued on page 31)

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STOPPING CORNEAL EROSION With Amniotic Membranes

This collagen-rich tissue is emerging as a new method for managing EBMD and recurrent corneal erosion. How does it perform clinically? *By Richard B. Mangan, OD*

Epithelial basement membrane dystrophy (EBMD) also known as map-dot-fingerprint dystrophy or Cogan's microcystic dystrophy, is a bilateral anterior corneal degeneration characterized by grayish map-like lines, possibly accompanied by microcysts, within a thickened corneal epithelium. Unlike most dystrophies that typically show clear deterioration or progression, clinical findings associated with EBMD are often variable. It is not uncommon for EBMD to be discovered during anterior segment surgery, as the diseased epithelium can become loose, irregular or even erode. Patients who complain of fluctuating or blurry vision may be experiencing the effects of EBMD, as it predisposes patients to recurrent corneal erosion (RCE), which is known to impact vision.

RCE is a relatively common disorder in which a segment of the outer epithelial layer of the cornea tears or becomes loose, often resulting in severe pain and secondary tearing, epiphora, rhinorrhea, redness and photophobia. These symptoms are most often present during sleep or upon awakening, and are usually linked to previous trauma (i.e., corneal abrasion), corneal dystrophy (i.e., EBMD, lattice, granular, Reis-Buckler) or a combination of both. Patients presenting with RCE will report a history of abrasion or trauma roughly 65% of the time.[1] Comparatively, epithelial basement membrane dystrophy is by far the most common corneal dystrophy and is associated with RCE approximately one-third of the time.[2] However, RCE may also occur spontaneously without any identifiable risk factors.[3]

Over the years, a number of treatment modalities have been proposed and used clinically to manage EBMD and/or recurrent corneal erosions: antibiotic drops and ointments, lubricants, topical steroids, hypertonic drops/ointments, autologous serum, bandage contact lenses, punctal plugs, platelet- or albumin-rich tears, oral doxycycline and vitamin C supplements. Additionally, surgical options such as debridement, anterior stromal puncture, burr or brush therapeutic keratectomy (BTK) and phototherapeutic keratectomy (PTK) can also be used if noninvasive methods are ineffective.

An increasing amount of anecdotal evidence released in recent years, however, supports the use of amniotic membrane tissue as a new treatment method for RCE.

PATHOGENESIS OF RCE

The corneal epithelium—like the cornea itself—is multilayered: the column-shaped basal cells that make up the deepest layer are covered by several layers of polyhedral-shaped wing cells and three to four superficial layers of flattened squamous cells. Each of these layers is continually undergoing mitosis, with basal and wing cells migrating anteriorly as squamous cells slough off in the tear film. Additionally, the basal epithelium also produces and adheres to its underlying basement membrane using an adhesion complex made up of hemidesmosomes and type VII collagen-anchoring fibrils.[4]

Sometimes, due to trauma, dystrophy or both, an abnormal deposition of the epithelial basement membrane can disrupt this adhesion complex.[4] Believed to be the main contributing factor to RCE, this results in a thicker, multilaminar membrane that is usually misdirected into the epithelium, causing irregularity and vision degradation.[5]

ABOUT THE AUTHOR

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Inflammation has also been implicated as a key contributor to recurrent corneal erosion syndrome.[6] RCE patients tend to show increased levels of polymorphonuclear neutrophils (PMNs) between cells and at the basement membrane interface.[7] Also, increased levels of matrix metalloproteinases (both MMP-2 and MMP-9) in epithelial cells and the tear film have been reported.[8] MMPs break down the extracellular matrix (laminin and type IV and VII collagen) of the basement membrane and adjacent tissue for remodeling purposes.

Fortuitously, amniotic tissue is also largely made up of the same extracellular components (type IV and VII collagen, laminin and fibronectin) that partially comprise the cornea.[9] Amniotic tissue also contains hyaluronic acid, which has direct and indirect (T-cell suppression) anti-inflammatory properties.[10] It is believed that these anatomical and physiological characteristics are responsible for the wound healing properties of amniotic membrane tissue.[11] This tissue exhibits antimicrobial properties and is said to promote epithelialization, suppress inflammation and inhibit scarring, without the potentially harmful side effects associated with topical and oral medications.[12]

INDICATIONS AND OPTIONS

Sutureless amniotic membranes are either cryopreserved (Prokera) or dehydrated (AmbioDisk or BioD Optyx) when processed and packaged.

Prokera (Bio-Tissue) is a class II medical device comprised of a cryopreserved amniotic membrane graft fastened to a plastic ring set; it must be kept or stored in the freezer. Its inner diameter is 16mm. The related Prokera Slim offers a thinner outer ring segment, yielding an inner overall diameter of 17.9mm, while the Prokera Plus is thicker (200µm) and recommended for more severe corneal compromise that would require more aggressive healing response.

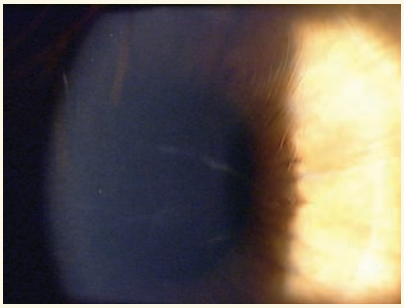

Fig. 1. Right eye—clinically significant EBMD (20/60 BCVA).

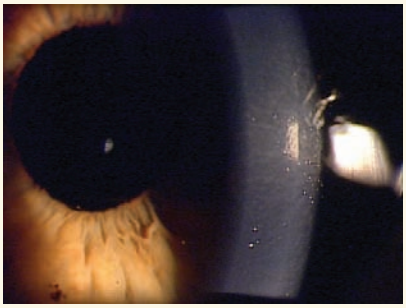

Fig. 2. Left Eye—Mild EBMD (20/25 BCVA).

AmbioDisk (IOP Ophthalmics) and BioD Optyx (BioD), on the other hand, are typically stored in a controlled room environment, but can be refrigerated. After the dehydrated amniotic membrane is placed on the eye, a soft bandage contact lens is used to secure its placement. IOP Ophthalmics offers the Ambio 2 (35µm thick) and the Ambio 5 (100µm), both with a diameter of 15mm. BioD Optyx comes in two disc sizes (12mm and 15mm) with a central thickness of 40 to 60 microns.

Aside from EBMD and RCE, sutureless amniotic membrane transplantation has also been found to be useful in the management of a wide array of other corneal, conjunctival and ocular surface conditions, including: acute Stevens-Johnson syndrome/TEN, acute burns, neurotrophic defects or persistent corneal epithelial defects, filamentary keratitis, microbial keratitis, VKC, bullous keratopathy, Salzmann's nodular degeneration, dry eye syndrome or recalcitrant SPK, oculoplastic procedures, and non-healing epithelial defects after PRK/PTK.[13-18]

Amniotic membrane grafts are also sometimes used in conjunction with ophthalmic surgical procedures, such as: SPK, corneal perforation, high-risk corneal transplantation, pterygium removal, band keratopathy, scleral melts, limbal graft for partial or total stem cell deficiency, conjunctivochalasis or conjunctival reconstruction, and glaucoma surgery.[18-20]

CASE REPORT: AMNIOTIC MEMBRANE FOR VISUALLY SIGNIFICANT EBMD

A 63-year-old Caucasian male presented with the primary complaint of blurry and distorted vision in his

Release Date: October 2014

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Goal Statement: This course reviews the relationship between epithelial basement membrane dystrophy (EBMD) and recurrent corneal erosion (RCE), and discusses the use of sutureless amniotic membrane for visual distortion related to RCE in EBMD.

Faculty/Editorial Board:
Richard B. Mangan, OD

Credit Statement: COPE approval for 1 hour of CE credit is pending for this course. Check with your state licensing board to see if this counts toward your CE requirements for relicensure.

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Disclosure Statement: Dr. Mangan has no financial disclores relevant to this course.

right eye. He reported symptoms started soon after he underwent cataract surgery and indicated that, visually, it was comparable to looking through cellophane. He was referred in for a surgical consult for clinically significant EBMD after medical therapy (Refresh artificial tears and Muro 128 ung QHS) had proven ineffective.

Best corrected entrance acuities were 20/60-2 (PH 20/30+2) and 20/25 (PHNI), respectively, and he exhibited diffuse map-dot-fingerprint changes to the epithelium OD >> OS (*Figures 1 and 2*), which was visible on slit-lamp examination. Oculus corneal topographical analysis confirmed surface irregularity consistent with EBMD (*Figure 3*), while wavefront aberrometry revealed clinically significant higher-order aberrations with a root mean square (RMS) value of 0.9 (for reference, normal is 0.3 or less).

After discussing the pathogenesis of recurrent corneal erosion syndrome and the risks, benefits and surgical alternatives, a joint decision was made to move forward with debridement and amniotic membrane transplant using Prokera.

Once the eye was appropriately anesthetized using Tetravisc, the corneal epithelium was gently debrided, leaving a residual 8mm epithelial defect. Preservative-free artificial tears and antibiotic drops were instilled prior to insertion of the amniotic membrane. Once the ring was removed from its sterile packaging, the amniotic tissue was irrigated using sterile saline and then placed on the right eye uneventfully. Slit-lamp examination confirmed adequate centration with normal lid tautness. Transpore tape was applied to the superior lid to aide in ring retention.

The patient was prescribed Polytrim antibiotic drops QID OD and hydrocodone 10/500mg. Before discharge, he was instructed to call our office should he experience any significant pain or discomfort. Additionally, he was told to avoid underwater activity or the operation of motor vehicles or other heavy equipment, as he can expect his vision to be blurry and depth perception to be temporarily compromised while the membrane is in place.

The patient returned for his scheduled follow-up one week following debridement and Prokera application. He reported there was significant discomfort during the first night, but that the pain resolved by the second day. He also reported intermittent foreign body sensation and tearing with epiphora since his treatment. His entrance acuity was 20/300 (PH 20/80).

The Prokera ring segment was removed uneventfully at the slit-lamp and the cornea showed complete reepithelialization with only trace haze. Vision was reassessed after ring removal and lubrication. It measured 20/80 (PH 20/30-2). The patient was started on Lotemax gel QID OD and Muro 128 QHS OD, and his Polytrim antibiotic drops were discontinued. His next follow-up was scheduled for one week later.

At his two-week follow-up appointment, his vision had improved to 20/30+ acuity; by one month, he refracted at 20/20- OD. He reported no residual glare or foreign body sensation, and slit-lamp examination confirmed a smooth epithelium and no residual stromal haze. Topical steroids were discontinued and he was asked to continue his Muro 128 ointment at bedtime until he returns for another follow-up with his family optometrist in six months.

MANAGING POST-OP DISCOMFORT

It is important to note that most patients experience some discomfort the night following the procedure and into the next morning. This is mostly due to the large epithelial defect created from the debridement rather than the placement of the amniotic membrane. Patients are instructed to call our office if the discomfort continues for greater than 24 hours, as this may be related to a decentered ring segment. It is also reasonable to proactively schedule the patient for a one-day postoperative visit if there is any concern about delayed decentration after ring has been applied.

In most cases, after centration has been confirmed at the slit-lamp, we apply Transpore tape across the breadth of the upper eyelid, bordering the lid crease. This keeps the interpalpebral fissure width small, decreasing the risk of ring decentration or escape. Because the lids are

Table 1. Initial Treatment Success Rates Reported For RCE

Authors	Treatment	Technique	# of Eyes	Success Rate
Buxton & Fox	Debridement		13	85%
McClean et al.	Anterior Stromal Puncture	20-gauge needle	21	86%
Tsai et al.	Anterior Stromal Puncture	Nd:Yag	33	85%
Buxton & Constad	Superficial Keratectomy	Diamond Burr	33	97%
Soong et al.	Superficial Keratectomy	Diamond Burr	54	94%
Hodkin & Jackson	Superficial Keratectomy	Amoils Brush	23	88%
Maini & Loughnan	Phototherapeutic Keratectomy	Excimer Laser	76	89%

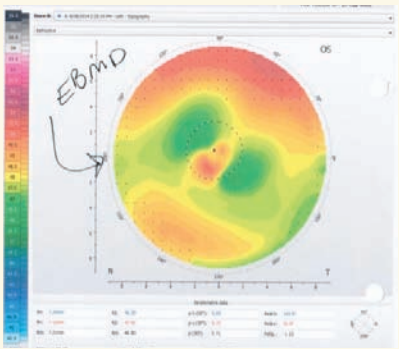

Fig. 3. Abnormal topography OD secondary to epithelial basement membrane dystrophy.

not taped completely shut, patients are still able to deliver topical antibiotics and lubricants uneventfully throughout the day.

The ring segment often causes foreign body sensation; if a patient returns complaining of significant discomfort, it is important to look for decentration of the ring. Sodium fluorescein dye can be instilled to evaluate not only the epithelial defect, but the integrity of the amniotic tissue. If centration seems to be the issue, repositioning and partial tarsorrhaphy are sometimes warranted to improve stability.

GENTLE DEBRIDEMENT PLUS MEMBRANE USE VS. SUPERFICIAL KERATECTOMY

Conventional medical therapy for recurrent corneal erosion syndrome is associated with a high recurrence rate.[21-23] While surgical intervention is more effective for refractory cases, demonstrating an 85% or higher initial treatment success rate (*Table 1*), there may be a greater risk of scarring over the visual axis or an unwanted change in refractive error with surgery.[24,25]

Research performed at the Ocular Surface Center in Florida suggests a comparable success rate when the Prokera ring is used in conjunction with debridement. In a small study, Huang, Sheha and Tseng studied the effects of debridement and Prokera placement for RCE in 11 eyes by a single surgeon. Ten of the 11 eyes were symptom-free during the mean follow-up period of 13.7 +/- 2.2 months, with reepithelialization occurring between days four through seven.[26]

In our experience, epithelial debridement with Prokera has been a reasonable approach to managing visual symptoms secondary to EBMD/RCE syndrome. Prokera may be stored in-office, making it readily available for either planned or untimely ocular urgencies. Its documented wound healing properties warrant its consideration for nonsurgical intervention when conventional medical therapy has not met expectations for you or your patient. RCCL

The author wishes to acknowledge the contribution of Gary Wörtz, MD, who provided the case report data.

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AMNIOTIC MEMBRANES

CE TEST

1. Which sutureless amniotic membrane comes cryopreserved?
a. Prokera Slim
b. Ambio 2
c. Ambio 5
d. Both B & C

2. RCE occurs secondary to trauma or abrasion what percent of the time?
a. 10%
b. 25%
c. 65%
d. 90%

3. Which of the following is NOT believed to contribute pathogenically to recurrent corneal erosions?
a. Increased polymorphonuclear leukocyte activity
b. Abnormal deposition of the epithelial basement membrane
c. The presence of hemidesmosomes
d. Over-expression of matrix metalloproteinases (MMPs)

4. Based on previous reports, what treatment modality is more likely to show refractory symptoms?
a. Phototherapeutic keratectomy (PTK)
b. Oral doxycycline plus topical steroids
c. Prokera
d. Anterior stromal puncture

5. Prokera is a self-retained sutureless medical device that promotes corneal wound healing. What class device is it?
a. I
b. II
c. III
d. IV

6. Which of the following sutureless amniotic membranes must be stored in the freezer?
a. AmbioDisc
b. BioD Optyx
c. Prokera
d. Both A & B

7. How many days does it take (approximately) for reepithelialization to occur after corneal debridement plus Prokera?
a. 1-2 days
b. 4-7 days
c. 10-14 days
d. 21 days

8. The Prokera ring design offers a number benefits when managing RCE. Which of the following is NOT considered one of them?
a. Can be stored in office and used immediately PRN.
b. It's sutureless.
c. Patients do not have to be seen for a full month after insertion.
d. Decreased risk of inducing an unwanted change in refractive error when compared to phototherapeutic keratetomy.

9. Which of these is NOT an expected side effect of Prokera?
a. Foreign body sensation
b. Blurry vision
c. Having to use a second Prokera in cases of severe inflammation
d. Anisocoria

10. Which is considered FALSE in association with Prokera ring use?
a. Narcotics should be prescribed as wearing the Prokera ring can be quite painful.
b. QID dosing of an AB drop is adequate for RCE when the Prokera ring is in place
c. Epithelial defects can be adequately viewed using NaFl while Prokera is in place
d. A temporary tarsorrhaphy is sometimes needed to help centration of the Prokera ring

Examination Answer Sheet

Valid for credit through October 1, 2017

This exam can be taken online at www.reviewofcontactlenses.com.
Upon passing the exam, you can view your results immediately.
You can also view your test history at any time from the website.

Stopping Corneal Erosion With Amniotic Membranes

Directions: Select one answer for each question in the exam and completely darken the appropriate circle. A minimum score of 70% is required to earn credit.

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1. Ⓐ Ⓑ Ⓒ Ⓓ
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1 = Excellent 2 = Very Good 3 = Good 4 = Fair 5 = Poor

Rate the effectiveness of how well the activity:

11. Met the goal statement: ① ② ③ ④ ⑤
12. Related to your practice needs: ① ② ③ ④ ⑤
13. Will help you improve patient care: ① ② ③ ④ ⑤
14. Avoided commercial bias/influence: ① ② ③ ④ ⑤
15. How would you rate the overall quality of the material presented? ① ② ③ ④ ⑤
16. Your knowledge of the subject was increased:
○ Greatly ○ Somewhat ○ Little
17. The difficulty of the course was:
○ Complex ○ Appropriate ○ Basic

How long did it take to complete this course?

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① SS # ___ - ___ - ___

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Business Name

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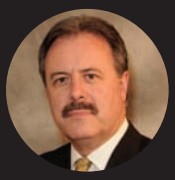
By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature _____ Date _____

Lesson 110667 RO-RCCL-1014

By James Thimons, OD



Containing the Epidemic: Complex Keratoconjunctivitis

The rise of an advanced form poses serious risks to patients. Here's how to get it under control—in the cornea and in the clinic.

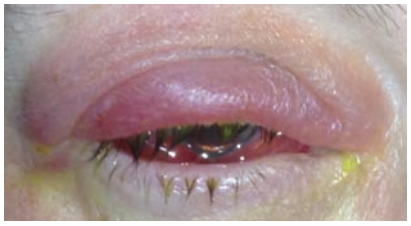
With the fall season upon us, the potential for adenoviral keratoconjunctivitis (EKC) to present in the office increases dramatically. While the etiology of the disease and its seasonal impact has long been known, recently there has been a significant increase in both the prevalence and severity of epidemic keratoconjunctivitis, one of the forms of the disease, making its management significantly more challenging.

DETECT AND DISTINGUISH

Singularly, the most important aspect of any treatment is to recognize the presence of the disease and use that knowledge to guide appropriate therapy. A new point-of-care system called AdenoPlus (Rapid Pathogen Screening) permits clinicians to accurately diagnose infectious EKC and differentiate it from many alternative etiologies that can have similar presentations. The system is easily deployable in the office and yields extremely high levels of sensitivity and specificity to the presence of the virus in a patient's tears.

Capable of detecting all serotypes of the viruses most commonly found in North America, AdenoPlus is particularly sensitive to serotypes 8 and 19.

Typically, a presentation of EKC is relatively mild, with patients showing classic symptoms of hyperemia, tearing, foreign body sensation, subepithelial corneal infiltrates



and minor lid edema. Historically, these symptoms are treated with standard regimens, including topical steroids, betadine rinse, ganciclovir, cool compresses and tear supplements. In the last two years, however, a more complex type of infectious disease has presented, with a morbidity that has been profound in some patients. Management of this variant—complex EKC—has proved more challenging due to both its intensity and duration.

The complex EKC patient presents with significantly greater intensity of disease, including marked periorbital involvement that can include notable spontaneous hemorrhaging, as well as pseudomembranous formation. Additionally, the nummular keratitis typically seen with EKC is much more dramatic and can frequently reduce acuity to the 20/100 to 20/200 range—markedly greater than the 20/20 or 20/25 levels typically seen with the disease. The lid involvement can also be associated with bacterial superinfection and preseptal cellulitis.

INTERVENE AGGRESSIVELY

Straightforward and simple to use, betadine has become a relative standard of care for many clinicians dealing with milder cases of EKC. I personally use non-alcohol-based betadine, which can be obtained in either swab or drop application modalities.

A typical procedure is as follows: first, I instill several drops of topical anesthetic and apply the betadine to both the upper and lower cul-de-sacs. I then wait several minutes while the betadine takes effect before rinsing it from the ocular surface with artificial tears and instilling several drops of topical steroid to decrease the somewhat inevitable foreign body sensation that the patient presents with following application.

The use of ganciclovir 0.15% (Zirgan, Bausch + Lomb) is also relatively common, although the clinical science surrounding it is somewhat anecdotal in nature. The first study presented a cohort of just 18 subjects, but demonstrated significant clinical improvement compared to nonintervention, which stimulated the current increasing use of this protocol. Zirgan is used five times per day, and is most effective when initiated within three to four days after the onset of clinical symptomatology. In the more complex cases presented to the office last year, however, Zirgan seemed notably ineffective in managing ocular symptomatology or diminishing the duration or intensity of the disease.

With this recent shift in EKC severity, several traditional diagnostic elements have changed dramatically. First is the bilaterality of the presentation. Traditional thought

holds that EKC is a bilateral disease and that other viral entities such as HSK/HZK are unilateral. However, the last two EKC seasons showed over 90% of the patients with RPS-positive findings having 4+ unilateral disease state with no involvement whatsoever of the fellow eye after four to six weeks of follow-up in most patients.

A second significant variation was the rate of bacterial superinfections that presented as preseptal cellulitis. This is differentiated by the level of pain/tenderness on palpation across the lid and the turbidity or tenseness of the tissue. In typical viral disease, the edema is soft and rarely has associated pain on palpation. Of the more than 70 patients who demonstrated severe clinical findings, 18 had concurrent preseptal cellulitis. When managing preseptal cellulitis, I prefer to use a standard penicillin, such as Augmentin 875mg PO BID for 10 days, in combination with hot compress therapy for the first several days to bolster the impact of the antibiotic on the bacterial superinfection. If the patient has a penicillin allergy, either assumed or noted, the use of a first- or second-generation cephalosporin is preferable in light of its excellent Gram-positive coverage.

Another important point when evaluating more severe cases is the need for a thorough examination of the inferior and superior fornices for the presence of pseudomembranous changes. Pseudomembranes often form within the first several days of onset, and will persist and increase if left untreated during the acute phase of the illness. Therapy is directed toward debridement and then subsequent intensive steroid therapy to prevent recrudescence of the lesion. My typical approach is to place several drops of anesthetic in the eye, then soak a cotton swab with phenylephrine and apply it directly to the site. After three to five minutes, a relative hemostasis is achieved that will allow for easier removal of the membrane.

In patients in which the membrane is loosely adherent, a hard cotton swab can sometimes be used to remove the tissue; however, in most cases, a forceps removal is required to tease out the delicate traction that takes place as these lesions develop and cause folding of the conjunctival tissue into layers.

My general preferred technique when there are cicatricial changes present is to use a blunt-tipped element, such as a punctal dilator, to slowly splay the folds open without producing damage to the underlying vascular bed. Following that, I will use forceps to gently tease away the membrane. If the tissue is severely embedded into the conjunctiva, I will try to remove as much as I can without significant damage, then treat the patient aggressively during the next 24 hours with topical steroids to melt down the membrane and allow for easier removal the second day. Membranes on the tarsal plate of the superior lid are sometimes extremely difficult to tease away and, as such, should be managed consecutively over several days.

Following removal, I place the patient on a high potency topical steroid (typically Q1 or Q2 hours) for the next 24 hours, and have the patient return either daily or every other day until the membranes are no longer forming and I have completed their removal. This usually involves one or sometimes two visits; however, some individuals in

How to Stop an Outbreak

While managing the ocular complications is a critical part of the success in the disease state, the most significant component of good disease management is infection control, both in the community and within the practice. Be mindful of potential transmission by office equipment like tonometer tips and slit-lamp chin rests.

Due to the severity of last year's outbreak, we instituted a universal precaution policy in which any patient who presented with a red eye was isolated until proof with RPS testing was completed. If they tested positive, the room was thoroughly sterilized before further use by another patient. All contact with individuals with red eye presentation was also managed with sterile gloves and disposable sterile equipment to decrease the possibility of transmission within the office.

Interestingly, while Zirgan was minimally effective in treating the severe cases, a new protocol in which I prescribed Zirgan for family members of patients with confirmed disease, combined with good home hygiene and infectious disease protocols, was unexpectedly successful: I did not have a single family member of a confirmed infectious patient develop the disease during our treatment periods.

last year's group of patients required four to six over the course of eight to 10 days of treatment.

Managing the patient's nummular keratitis can also be particularly challenging in complex cases. The level of steroid use is intensive and patients have to be monitored for typical side effects associated with that treatment, but abrupt cessation can trigger rebound nummular keratitis. Adding a topical antihypertensive agent can mitigate concerns related to a short-term rise in IOP.

In cases of rebound nummular keratitis, the recurrence can actually exceed the initial treated disease state in some patients. Several individuals in last year's group of patients developed calcific-like deposits around the virions in the cornea after cessation of steroid therapy, and subsequently had to be restarted on steroid treatment that has persisted in some instances for several months following the initial disease state. Two of these patients had severe enough deposits even following aggressive steroid treatment that PTK is being considered in order to reduce the scar formation and improve visual function.

The management of complex EKC also presents one of the rare opportunities for clinicians to become infected by their patients. This is a significant problem, and in this last year's epidemic, I treated numerous medical professionals for EKC who been exposed in-office but had not taken appropriate precautions to prevent disease acquisition (see *"How to Stop an Outbreak"*).

Your role in management—at both the individual patient level and also as an expert resource to the health care community—should be to educate patients on their risk to others, and the need for appropriate hygiene and avoidance of contact with family, friends and coworkers. This is a critical component in minimizing its impact and decreasing the long-term complications of the disease. RCCL

DRY EYE: CAN YOU TACKLE THESE TOUGH CASES?

(Continued from page 23)

Dr. Brujic: Unlike the others, Dr. Brujic believes surgery isn't required, despite the conjunctivochalasis. He suggests maintaining the Restasis BID and adding heat therapy (e.g., a Bruder Mask) in the evening to increase compliance. "Often, people just apply a warm washcloth to the eyes for a few minutes, which is inadequate in my experience," he says.

Also determine if the patient's current artificial tears are suitable for her type of dry eye. For example, if she is using a store brand such as Visine, Dr. Brujic would discontinue it and instead prescribe one that is more appropriate to her condition.

He would also order further testing, specifically InflammaDry on each eye to determine if the MMP-9 levels are greater than 40ng/mL, and ask about any nutritional supplements she may be taking.

"Assuming she is not taking anything, I would start her on an appropriate ocular nutrient that would support improvement in tear film function, such as EZ tears by ZeaVision," Dr. Brujic says.

Finally, Dr. Brujic would test her four-to-six weeks later with InflammaDry. Depending whether improvement is noted, he would either keep her on the prescribed regimen or add a topical steroid such as loteprednol gel QID for a month. He would then ask to see the patient again for further evaluation.

Dr. Shovlin: "Conjunctivochalasis should be distinguished from aqueous-deficient dry eye and recognized as a significant masquerader for dry eye, as they often have similar symptoms and signs," explains Dr. Shovlin, who submitted this case. When the conjunctiva is loose enough, it can occlude the puncta and cause epiphora. Such a condition can result in mechanical irritation and conjunctival redness that affects many patients, especially those of the older population when the conjunctiva loses its firm attachment to Tenon's membrane.

Dr. Shovlin treated the patient using Prolensa HS, a topical NSAID. However, he cautioned, some patients will need conjunctival resection and, if large areas are excised, an amniotic membrane graft may even be needed. RCCL

By Mile Brujic, OD, and Jason Miller, OD, MBA

Treating Dry Eye—With Contacts

Commonly discouraged in cases of eye irritation, contact lenses can sometimes provide relief to patients with ocular surface disease.

As important as visual acuity surely is to contact lens wearers, it's fair to say that comfort matters even more. Roughly 50% of contact lens wearers reported lens comfort issues when questioned during a 2002 study, so it's not surprising that discomfort is considered the number one reason for the discontinuation of lens wear.[1,2] For this reason, we are constantly striving to keep the ocular surface healthy and conducive to comfortable contact lens wear.

Contact lens-related dryness is a fairly common phenomenon characterized by the appearance of dryness symptoms only during contact lens wear. However, there are times when an underlying ocular surface condition, such as dry eye disease, can be the root of the problem causing the lens intolerance. In these cases, it's fair to wonder how an already dysfunctional tear film could tolerate the presence of a lens without even further disruption. In fact, there are some instances in which dry eye can be treated using contact lenses.

CHOOSING A LENS

When the ocular surface is compromised, much of the discomfort our patients feel derives from mechanical trauma as the eyelid passes over the weakened corneal surface. As such, there are benefits to placing a contact lens upon the ocular surface: it immediately decreases pain sensations because it acts as a shield over the irritated cornea, allowing the epithelium to heal without the constant interference of the eyelid sweeping over the surface.

However, bandage contact lenses should be used with caution. If a patient's cornea is compromised due to an infectious etiology, placing a contact lens over an ulcerated cornea could harbor the offending organism, making the condition significantly worse.

While a number of lens types can be used as bandage lenses, silicone hydrogel lenses are a particularly common choice as they allow significantly more oxygen to reach the cornea, mitigating any hypoxic stress that could compromise corneal physiology. However, while these lenses are successful in blocking the lid's mechanical irritation of the cornea, they often do little to encourage healing in a patient with corneal compromise, and so must be combined with additional treatment methods.

An intervention gaining favor in recent years is to stimulate wound healing with amniotic tissue. In one method, a plastic ring anchors a cryopreserved amniotic membrane along the conjunctiva and holds the membrane against the cornea and conjunctiva. Another uses a dry amniotic membrane that is placed directly on the cornea. A bandage contact lens is then typically placed on the eye, which keeps the amniotic membrane in place against the compromised cornea.

Scleral lenses also exist as an alternative contact lens option for those exhibiting chronic dry eye with severe ocular surface damage. Typically, each lens is filled with non-preserved saline before being inserted onto the eye, where it provides a bath of continuous moisture to the compromised cornea. Additionally, the rigid lens material creates a smooth refracting surface, which is often absent in a severely compromised cornea. With an appropriate prescription, the lens may provide the patient with visual correction while simultaneously rehabilitating the surface.

Fitting scleral lenses for a severely compromised cornea as a result of dry eye relies on the same principles used to fit these lenses for any other patient. There are three major goals: (1) achieve a central corneal clearance between 100µm and 300µm, (2) keep the corneal region free of any contact with the lens, and (3) design a scleral landing free of impingement or compression—that is, one that conforms to the curvature of the conjunctiva and underlying sclera.

Considering these factors when dealing with your severe dry eye patients will not only help keep them in lenses but will also help you rehabilitate and protect some of your most severe cases of corneal compromise.

ALTERNATIVE THERAPIES

Several other treatment options exist that can be attempted prior to scleral lenses. Lacrisert, a hydroxypropyl cellulose ocular insert, can be placed in the inferior cul-de-sac, where it slowly dissolves over 24 hours, stabilizing the tear film and increasing tear break-up time. Another option, punctal occlusion, retains tears on the ocular surface and could be considered for patients

whose ocular surface inflammation has been controlled.

Autologous serum can also be used if the ocular surface is severely compromised. To create an autologous serum, the patient's blood is drawn and the serum is separated through centrifuge. The serum is then usually diffused with an artificial tear and placed in vials for patient use.

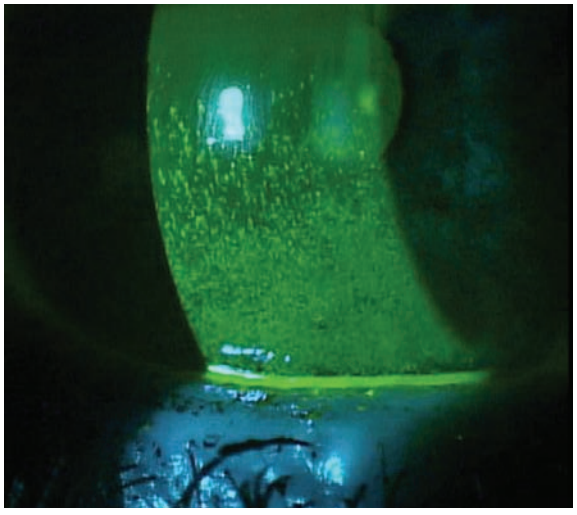


Fig. 1. Significant corneal staining in a patient with Sjögren's, fibromyalgia and rheumatoid arthritis.

CASE IN POINT

A 57-year-old female came in for a routine eye exam. She has Sjögren's syndrome, fibromyalgia and rheumatoid arthritis. She is currently wearing silicone hydrogel contact lenses as bandage lenses because of severe corneal compromise resulting from Sjögren's syndrome, as well as the need for corrective lenses. The lens parameters were: OD +5.00/8.6/14.0, OS +2.00/8.6/14.0. She was using a monovision approach, with the left eye adjusted for best near focus. She reported trying various soft lenses in the past, including daily disposables, but said her current lens modality offered the best handling, vision, comfort and resistance to deposits.

Even though these soft lenses functioned well for her, she nevertheless complained about fluctuating vision and uncomfortable lens wear. Symptomatic ocular surface dryness while wearing contact lenses was significantly better than how her eyes felt in the absence of lenses. To help control her symptoms, she was using Systane Ultra 1-2gtt BID-QID OU over her contact lenses. Upon physical examination, her corneas were remarkable for significant corneal staining of the inferior half of the cornea (*Figure 1*).

The patient was fit with scleral lenses with appropriate central and limbal clearance (*Figure 2*), and a suitable scleral landing zone. She was instructed on proper lens insertion, removal and care. The lenses were dispensed and she was seen one week later for follow-up. At that time, she reported significantly improved comfort and vision with the scleral lenses. She was able to wear the lenses for the whole day and only sporadically had to use artificial tears.

Upon lens removal, there was just a trace amount of corneal staining present (*Figure 3*). The patient will continue to wear these lenses for the foreseeable future.

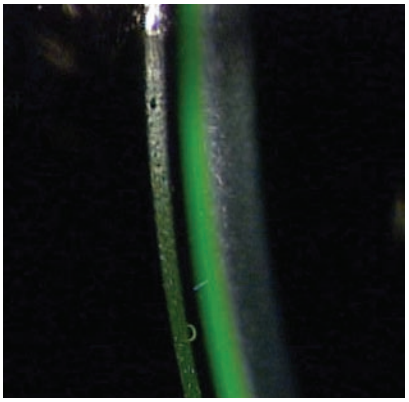


Fig. 2. A scleral lens was designed to address her corneal compromise.

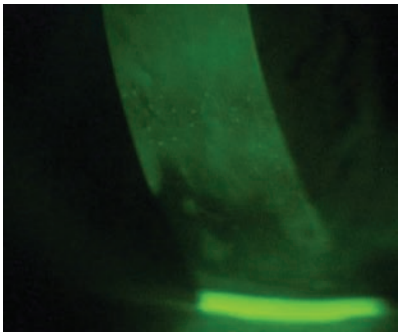


Fig. 3. After one week of wear, only trace amounts of staining remain.

Because dry eye can arise from many different potential causes, the best treatment method can vary. This example demonstrates the appropriate use of scleral lenses for severe ocular surface disease, but other causes may be best managed with soft lenses, or no lens at all. RCCL

1. Young G, Veys J, Pritchard N, Coleman S. A multi-centre study of lapsed contact lens wearers. Ophthalmic Physiol Opt. 2002 Nov;22(6):516-27.

2. The Definition and Classification of Dry Eye Disease: Report of the Research Subcommittee of the International Dry Eye WorkShop (2007). Ocular Surf. 2007 Apr;5(2):179-93.

Yet Another List

All successful doctors do these four things — do you?

I honestly don't think a single day goes by where I don't see something that talks about what I need to do to be more successful in the workplace. My inbox, news feeds and social media are inundated daily with list after list, with clickbait headlines that rely on superlatives and absolutes, like "Four Things You Should Never Ask Prospective Employees," "Five Words That Should Be in Every Email" and "The Six Best Ways to Do More With Less!"

Web sites like Buzzfeed have made the odious "listicle"—an article that's just a glorified list—a reality, churning out oversimplified light entertainment ideal for sharing on social media. In the professional realm, LinkedIn and other sites distribute plenty of them too. They've even become widespread enough to spawn a parody site, www.clickhole.com, from the people behind satirical news site The Onion.

My advice: ditch the list. Putting down that "Top Five" list could help you and your practice save time, money and energy.

UNLISTED

I stopped paying attention to nearly all of these listicles about a year ago. Ever since I stopped reading and using any of this "sage" advice, business has never been better. I doubt I can attribute the success solely to just the cessation of mindless reading, but it has certainly been liberating not to get bogged down with too many general, catch-all lists! Instead, here is my own personal list, "Four Things I Do With the Extra Time I Don't Waste Reading Lists About What I Should be Doing Differently."

1. I get more things done. Everyone has a seemingly never-ending to-do list, and I'm convinced there will always be more good ideas than there will be time to execute them. Therefore, I have committed to continually focus on the most important things right away, confident that I will eventually get to the other things later. And if I don't, that's OK—at least I got to the most important ones.

2. I spend more time focusing on the strategic direction of the company. First, because it's my job. As the chief dream officer at the Power Practice, it's up to me to lead the rest of my team and set the course for our future.

In your office, if you're the practice owner, it's your job to plan for your practice's future. Saying, "I want to grow my practice" isn't planning. I'm talking about having firm plans—concrete, actionable goals with a sound strategy to achieve them. That's your job and it takes time. Second, because now that I'm not wasting time reading lists, I actually have more time to get this important task done!

3. I enjoy myself more. You are probably already measuring a lot of things in your practice, including revenue, the number of established patients vs. new patients, the percentage of patients wearing contact lenses vs. glasses and staff productivity.

In addition to these conventional measurements, I always measure how happy I am doing what I'm doing. Yes, it's hard to quantify "happiness" but from time to time, I stop to catch my breath and ask, "Am I happy doing what I'm doing?" So far, the answer has been a resounding "Yes!" Keep that in mind as you work through this list. If you're not happy with your career situation or profession, try to make changes to fix that. If you can't, change careers. Yeah—that's hard. But we both know it's the right thing to do.

4. I focus more on what I want. Stop wasting time reading lists about what successful people do and start doing things that are important to *you*.

However, if you can't resist and you find yourself being suckered into another list—I'll admit happens to me occasionally—find the strength to move on after the first obvious point.

For example, I recently read an article about how to respond to negative online reviews, thinking maybe I'd find something valuable to share with our clients. The first point said to "make sure you monitor your reviews." This was beyond "Captain Obvious" for me and was enough to stop me from reading further. When the lead-in point is that clear, I recommend moving on to something more productive.

So, put this list down and get to work! RCCL

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REFERENCES: 1. Brennan NA. A Model of Oxygen Flux Through Contact Lenses, Cornea 20(1):104-108, 2001. **2.** Bergmanson J. Clinical Ocular Anatomy and Physiology. 14th ed. Houston, Texas: Texas Eye Research and Technology Center; 2007. **3.** Twenty-two subjects participated in a randomized, double-masked, contralateral eye study to evaluate water loss of Biotrue® ONEday, 1-Day ACUVUE MOIST, and 1-Day ACUVUE TruEye. After 4, 8, 12, and 16 hours of wear, lenses were removed and immediately weighed (wet weight). The lenses were then completely dried and reweighed (dry weight). The percent water loss was then calculated for each lens from the wet and dry weights.

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References: 1. Alcon data on file, 2011. 2. Eiden SB, Davis R, Bergenske P. Prospective study of lotrafilcon B lenses comparing 2 week versus 4 weeks of wear for objective and subjective measures of health, comfort and vision. Eye & Contact Lens. 2013; 39(4):290-294.

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