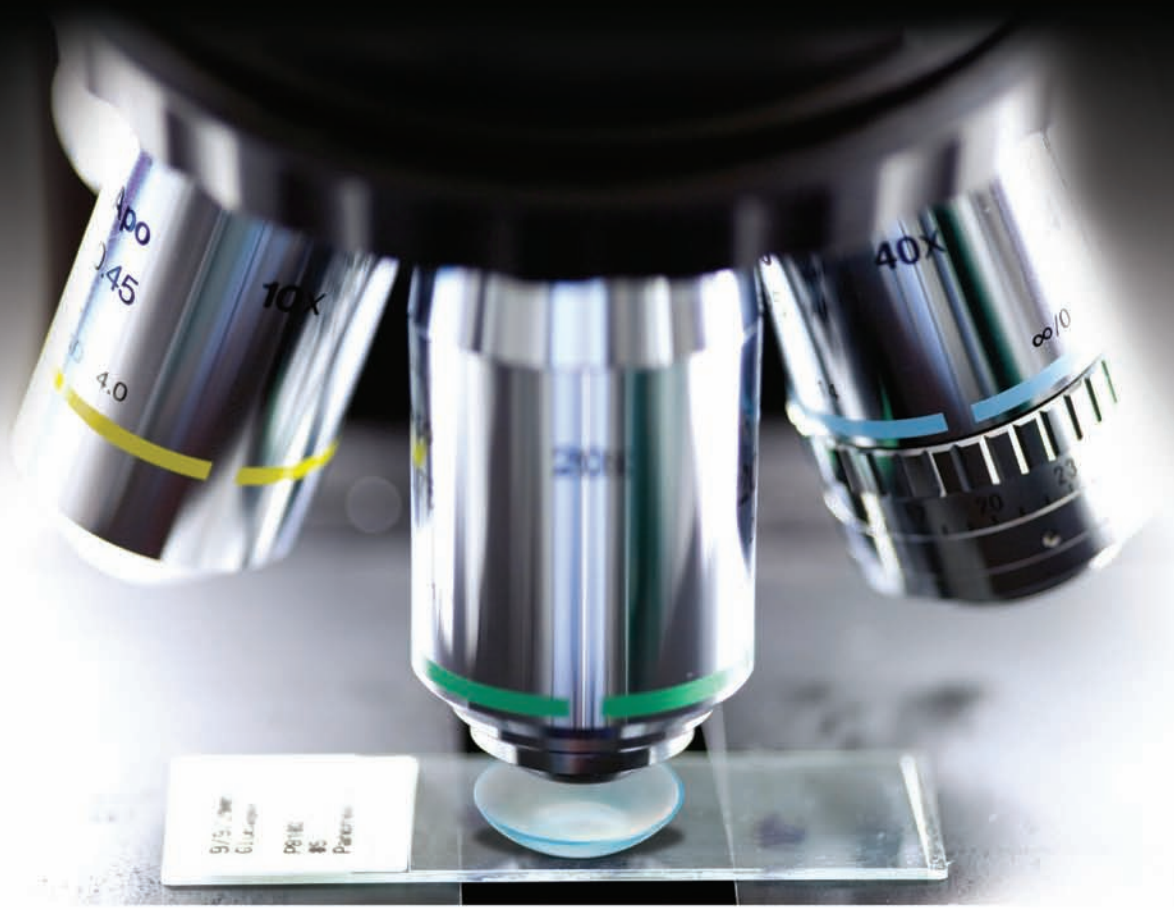
Review of Cornea & Contact Lenses

NOVEMBER 2012



RESEARCH ISSUE

INSIDE THIS ISSUE:

Supplement to
REVIEW® OF OPTOMETRY
November 2012

Earn 1 CE credit in this issue. See "A Wide-Angle View of Keratoconus," p. 15.

Compliant* Patients Come In For More Eye Exams.[1]

Alcon Can Help Bring Patients Back.

Alcon offers the DAILIES® family of daily disposable contact lenses and the AIR OPTIX® family of monthly replacement lenses. Multiple studies have shown that daily disposable and monthly replacement contact lens wearers are more compliant* than those who wear 2-week lenses.[2,3,4] Compliant patients also return for more eye examinations.[1]

Read more about this latest study, and see how Alcon can boost your practice, at myalcon.com/power-of-one

POWER OF ONE™

MORE POWER FOR GREATER SUCCESS

*Compliance with Manufacturer-Recommended Replacement Frequency (MRRF).

References: 1. Dumbleton KA, Richter D, Jones LW. Compliance with lens replacement and the interval between eye examinations. *Optom Vis Sci.* 2012;89 (E-abstract 120059). **2.** Dumbleton K, Woods C, Jones L, et al. Patient and practitioner compliance with silicone hydrogel and daily disposable lens replacement in the United States. *Eye & Contact Lens.* 2009;35(4):164-171. **3.** Yeung KK, Forister JFY, Forister EF, et al. Compliance with soft contact lens replacement schedules and associated contact lens–related ocular complications: The UCLA Contact Lens Study. *Optometry.* 2010; 81(11):598-607. **4.** Dumbleton K, Woods C, Jones L, et al. Comfort and Vision with Silicone Hydrogel Lenses: Effect of Compliance. *Optom Vis Sci.* 2010;87(6):421-425.

See product instructions for complete wear, care, and safety information.

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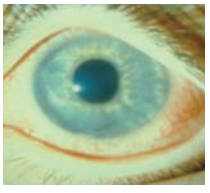
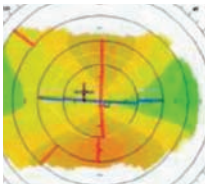
Research Issue

ON THE COVER





Departments

VOL. 149, No. 8

In The News

• The **Global Specialty Lens Symposium** will be held January 24-27, 2013 at the Rio All Suites Hotel and Casino in Las Vegas. The 2013 conference will include the fundamentals pre-conference, presentations by field experts, demonstrations of cutting-edge products, as well as scientific papers and posters and networking opportunities. For more information, visit www.GSLSymposium.com.

• **GP Specialists**, a custom soft and gas-permeable contact lens laboratory, received FDA clearance to begin manufacturing made-to-order soft contact lenses using the Definitive silicone hydrogel (Contamac). For more information, visit www.gpspecialists.com.

• A new **EZ-Exchange** program allows practitioners to make lens adjustments without having to return the original lenses, according to Alden Optical. When fitting adjustments are needed, practitioners can order new lenses and dispose of the originals. The new policy was designed to maintain efficiency and decrease shipping and handling costs. For more information, visit www.aldenoptical.com.

• **Minute-to-Fit 2.0** is a new fitting approach for Duette lenses (SynergEyes): The rigid center is fit like a rigid gas-permeable lens and the soft skirt is fit like a soft lens. The fitting does not require fluorescein. For more information, visit www.synergeyes.com/duette.html.

• A new **13-minute tutorial** offers eye care practitioners and staff strategies for improving the sales of annual supplies of contact lenses, according to ABB Concise. The tutorial highlights the importance of selling annual supplies for patient retention and office efficiency, as well as the patient's savings and compliance. The lesson presents scenarios such as how to handle objections and how to provide scripts. For more information, visit www.abbconcise.com.

Several New Lenses to Hit the Market

The 2012 Academy of Optometry meeting in Phoenix was the venue of choice for industry professionals to provide a glimpse into the ever-expanding contact lens market. Keep an eye out for these new additions:

• Baus ch + Lomb announced FDA approval of the company's new premium daily disposable contact lens, Biotrue OneDay. The lens offers high water content and delivers more oxygen than a traditional hydrogel, without using silicone. Biotrue OneDay was designed to alleviate the blurriness experienced by some lens wearers toward the end of the day that is thought to be caused by lens dryness.

• Launched at AAO 2012, the Astera (Alden Optical) multifocal toric soft lens features dual elliptical stabilization for improved orientation and rotational stability, and center-near multifocal optics with a large stabilized zone at near and distance. Tom Shone reported that this unique approach to stabilization is available in custom prescriptions and multiple replacement cycles.

• The Onefit (Blanchard) mini-scleral lenses, which completely vault the cornea, are designed for young contact lens wearers, sports active adult and youth populations, as well as dry eye and GP-intolerant patients. According to Richard Dorer of Blanchard, the unique design delivers extended hours of comfortable wear and improved vision performance due to a larger posterior optical zone.

• Alcon is developing a new daily disposable contact lens that will feature a core of silicone hydrogel material with high oxygen transmissibility and a surface of water-loving polymer chains with essentially no silicone, reducing friction. A unique "water gradient" design varies the water content from 33% at the core to more than 80% at the surface. According to the company, the result improves end-of-day comfort without compromising oxygen transmission.

A Quick Conjunctivitis Confirmation

Need reassurance in differential diagnosis of conjunctivitis? A new in-office test may help. AdenoPlus (Nicox) works by detecting adenovirus, which is responsible for 90% of all viral conjunctivitis and 25% of acute conjunctivitis cases. The test has 90% sensitivity and 96% specificity, and takes two minutes to complete a four-step process, according to the company.

For more information, visit www.nicox.com.

Review of Cornea & Contact Lenses

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Greater Precision in Dry Eye Diagnosis?

By measuring tear lactoferrin—the only available diagnostic biomarker to determine aqueous deficiency—TearScan (Advanced Tear Diagnostics) can provide a one-step ocular diagnostic test. The company believes that tear fluid holds the source material needed to identify aqueous deficient dry eye, assist in diagnostic differentiation between ADDE and evaporative dry eye, and develop effective treatments. TearScan also provides data that enables the provider to grade the level of dry eye severity and monitor the effectiveness of treatment. The test, which uses reflectance photometry, takes approximately four minutes and provides measurements with 98% specificity, the company says.

For more information, visit http://teardiagnostics.com.

New Lotemax Gel in the Works

The FDA has approved a new drug application for Lotemax (loteprednol etabonate, Bausch + Lomb) in the 0.5% gel drop formulation. Lotemax is used for the treatment of postoperative inflammation and pain following ocular surgery. Recommended dosage is one or two drops of the gel into the conjunctival sac of the affected eye q.i.d. from the first day after surgery through two weeks of postoperative care.

For more information, visit www.bausch.com.

Contact Lens Reserve May Aid Compliance

New data says that patients who keep an adequate supply of contact lenses handy tend to be more compliant with lens replacement schedules and are less likely to wear their lenses beyond the recommended interval. Researchers at Vistakon surveyed 958 two-month or monthly lens wearers from the United States and Canada. They collected weekly data including when lenses were replaced, how many lenses were kept on hand, and general perceptions of the wear experience.

For all wearers combined, 28.7% replaced their lenses on time when they had less than a six-month supply in reserve; one-third more, or 39.4%, replaced their lenses on time when they had more than a six-month reserve. On average, biweekly wearers replaced their lenses every 3.3 weeks, while monthly wearers replaced them at 5.6 weeks.

For more information, visit www.vistakon.com.

Advertiser Index

Editorial

By Joseph P. Shovlin, O.D.

The Persistent *Acanthamoeba*

Practitioners should stay abreast of current research and take a proactive approach to detecting and treating *Acanthamoeba* keratitis.

Just last month our group at the Northeastern Eye Institute confirmed another case of *Acanthamoeba* keratitis. Although the patient received an early diagnosis, he is still likely to experience significant morbidity and much anxiety associated with having this frightening condition. In fact, *Acanthamoeba* continues to have a relatively low attack rate with substantial geographic and seasonal differences.

Incidence rates range from one to 33 cases per million contact lens wearers, with a higher number of reported cases occurring during the summer months.[1-3] Scotland and South Korea report the highest national rates.[4]

The Disease

Although *Acanthamoeba* keratitis is an exceedingly rare infection, you may still find yourself facing such a case. Keep in mind that a timely diagnosis is crucial for the best outcome. Patients with *Acanthamoeba* keratitis often present with an early non-specific keratitis that progresses over time. Variable symptoms include eye pain, redness, blurred vision, light sensitivity and tearing. Epithelial signs include patchy involvement and a stellate or pleomorphic epitheliopathy.[4] Punctate erosion, an elevated dendritiform and a "bull's eye" lesion are possible. Stromal involvement can include a granulomatous, nonsuppurative infiltrate and radial neuritis. Ring infiltrates appear later and are not pathognomonic for *Acanthamoeba* infection.[4] Note: Any non-specific keratitis thought to be bacterial or viral that doesn't display a seemingly appropriate response to therapy should be reconsidered for rare diseases such as fungal and protozoan infections.

Today's Research

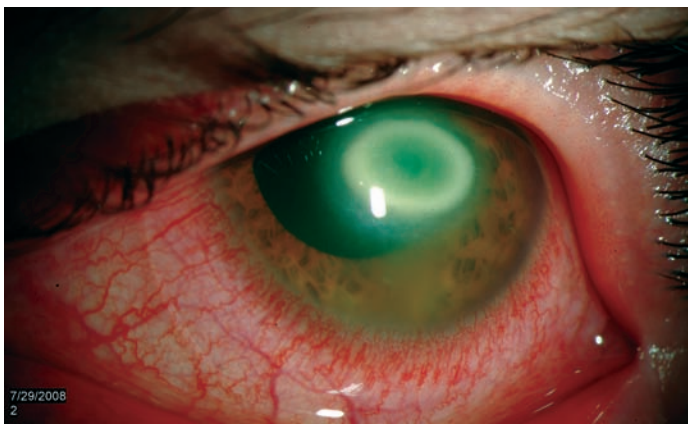
Two recently released studies take a close look at multi-state outbreaks, from 2008 through 2011, following the recall of a multipurpose disinfecting solution in 2007.[1,2] Experts anticipated that the rates of *Acanthamoeba* keratitis would fall significantly after the solution recall. Instead, a convenience sample with surveillance data collected from 13 U.S. ophthalmology centers and laboratories showed that *Acanthamoeba* keratitis cases remained higher than pre-launch levels.[1,2]

Surveillance monitoring of compounding pharmacies reported an increase in anti-amoebic medications ordered during the post-solution recall phase, which correlates with the data collected at the abovementioned sentinel sites.[1] Unlike the *Fusarium* outbreak, where the rates declined dramatically following a solution recall, the cases of *Acanthamoeba* keratitis did not rapidly decrease after the implicated solution was recalled. Remember, a recalled product is not always "unsafe" and it's crucial to continue to follow trends and set new baselines following any recall. Of particular note, heightened awareness and additional diagnostic techniques do not fully explain the persistent levels of new cases detected in the past few years.[1,2]

Risk Factors

Risk factors for *Acanthamoeba* keratitis include contact lens wear, a significant microdehiscence, repeated inoculation with contaminated solution or water, and host susceptibility.[4] According to the CDC, multiple contact lens hygiene practices are associated with increased risk for infection, including:

- Topping-off



Practitioners should be vigilant in diagnosing and treating *Acanthamoeba* keratitis.

(continued on pg. 9)

By Gary Gerber, O.D.

Reward Your VIPs

Give patients extra incentive to arrive on time, pay their bills and stay compliant with your recommendations.

The Transportation Security Association has unveiled a new "TSA Pre √" program to help frequent travelers quickly pass through the airport security screening line. Once vetted by the TSA and determined not to be a security risk, these select passengers can enter a special line and, to save time, do not need to take off their shoes or remove their computers from their bags. As a frequent traveler, I immediately signed up for this service.

For me, there is definite value in saving a few minutes and reducing the stress associated with traveling. To both the airlines and the TSA, my frequent travels essentially would categorize me as a good returning customer.

Do you have similar frequent flyers at your practice? Or, more accurately, do you have regular patients who could benefit from (and appreciate) any special services you might be able to offer?

The VIP Status

Start by having a conversation with your staff. Ask them to evaluate your current patients and answer the question, "If you could clone any of our patients, who would it be?," and ask why. Through this process, you will not only learn about your patients, but also find out what characteristics your staff most appreciates.

You will find that staff responses typically will be anecdotal: "Mrs. Jones is a great patient and I wish we had more just like her. She's super friendly, shows up on time for her appointments, is always complimentary, sends us lots of new patients, is a cheerleader for the practice, pays her bills on time, doesn't have any insurance discrepancies we need to deal with, is compliant and likes to learn about new products or services."

What did you learn from this conversation? You now have a list of attributes to help create your VIP list. In the above example, consider placing Mrs. Jones on the list of patients who should receive updates on new products. Then, when you get information on a toric, colored, daily disposable photochromic multifocal (I can dream, can't I?), Mrs. Jones will be the first to know.

It is most beneficial when more, not fewer, people are on board; the more people that join the VIP program, the more expeditious the entire experience will be.

Another suggestion is to create a list of patients who consistently arrive on time. You can offer these patients "prime time" slots—those that are customarily in high demand and are scheduled first.

Marketing the VIP Program

Once you have organized your VIP program, start marketing it to all your patients. Remember the TSA philosophy: It is most beneficial when more, not fewer, people are on board; the more people that join the VIP program, the more expeditious the entire experience will be. Consider implementing a referral system. Let all of your patients know that VIP service exists and is available to those who pay their bills on time, show high levels of compliance, refer others, etc. Market these services via email blasts, recall reminders, on-hold messages, social media sites and statement stuffers.

Ask your staff to generate excitement around the program. For example, if you know a new product will be coming to the practice soon, give your staff the OK to discuss it with your patients. They can help build anticipation: "Did you know that our practice will be one of the first in the area to get a new type of contact lens? Initially, it will only be available to our VIP patients, as we will have a very limited supply. Would you like to join our VIP program? I can put you on our list." Follow this introduction with an outline of the program's benefits and the eligibility requirements.

Keep in mind that this concept is not meant to discriminate against non-VIP patients. Rather, it's designed to reward those who have been most appreciative of your efforts to support them. RCCL


By Elyse Chaglasian, O.D., and Jill Autry, R.Ph., O.D.

A Toolbox Addition

A new Lotemax gel will soon offer easier patient handling, a lower preservative concentration and a more compatible pH level.

Because optometrists are closely involved with the pre- and postoperative surgical care of our cataract patients, it often falls to us to manage the inflammation and pain that commonly occur postoperatively, and steroids have long been the mainstay. Loteprednol etabonate (LE) 0.5% suspension (Lotemax, Bausch+ Lomb) has been extensively studied and, for over a decade, has been a recommended treatment for our postoperative patients due to its lesser propensity to raise intraocular pressure as compared to other corticosteroids like dexamethasone or prednisolone acetate.[1,2]

In 2011, the FDA approved a preservative-free ointment form of LE after multi-center studies concluded that the formulation was safe and effective for the control of postop inflammation and pain.[3]

On October 1, 2012, a gel formulation of loteprednol etabonate 0.5% was FDA approved. It will be available as a 10ml bottle. The launch date is yet to be determined. The gel is supposed to provide increased viscosity on the eye for better retention, which in turn would improve patient compliance by eliminating the need to shake the bottle prior to instillation. Also, the loteprednol gel contains glycerin, propylene glycol and a 0.003% concentration of benzalkonium chloride (BAK), compared to the 0.01% concentration of BAK in the suspension form, which should provide greater patient comfort.[4]

The Safety Trials

The safety and efficacy of loteprednol etabonate 0.5% gel was assessed in a multicenter, double-masked, parallel group, vehicle-controlled study at 20 American and two German sites.[5] A total of 407 patients were enrolled: 206 in the loteprednol etabonate 0.5% gel group and 201 in the vehicle group (which contained the exact concentration, amount and formulation of all the inactive ingredients and preservative, but without any loteprednol etabonate).

Eligible candidates were over the age of 18, not pregnant and with a potential visual acuity of 20/200 O.U. or better. Only patients with an anterior chamber reaction of Grade 2 or better on the first postoperative day were included. Subjects that were excluded were those who had the potential need for postoperative NSAIDs, systemic or ocular steroids, concurrent ocular therapy with immunosuppressants during the 18 days following surgery or within 30 days prior to the surgery, a history of generalized systemic disease or with severe ocular conditions, monocular patients, uncontrolled glaucoma or treatment for glaucoma in the fellow eye or a known sensitivity to the study drug or any of its components.

The study period was four weeks and required seven visits. Cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation was performed on the second visit. All patients received either the loteprednol etabonate gel or placebo (one to two drops used four times a day for 14 days). The patients were seen on postoperative days one, three, eight, 15 and 18. Compliance was assessed via a patient diary and by weighing the drug bottle.

Efficacy was determined by the complete resolution of anterior chamber inflammation and no pain on postoperative day eight. The secondary efficacy endpoints were complete resolution of anterior chamber cells and flare (individual and combined) at each visit, and the difference in change from baseline at each follow-up. Safety was determined by the incidence of adverse events, change in intraocular pressure, visual acuity, slit lamp and fundus findings.

The study results:[6]

- 31.1% of gel patients, compared to 13.9% of the vehicle group, showed complete resolution of anterior chamber inflammation.
- The gel patients had a statistically significantly greater

rate (75.7%) of Grade 0 pain vs. the vehicle group (45.8%).
- Mean intraocular pressure, via applanation, was similar between the two groups. One patient in the gel group experienced a significant increase in pressure that was not considered drug related because of a similar increase in the untreated fellow eye. One patient in the vehicle group had a 6mm Hg increase in pressure at day 15 that was potentially drug related.
- Fewer adverse events occurred in the gel group (16%) vs. the vehicle group (28.9%).
- Only 30.1% of the gel-treated patients required rescue medication (NSAIDs and/or corticosteroids) compared to 61.2% of the vehicle group

Lotemax gel appears to be safe, effective and well tolerated. Also, remember that loteprednol etabonate in alternate formulations (suspension and ointment) have been well studied, and deemed safe and effective in reducing postoperative pain and inflammation. Greater contact time and improved patient compliance would allow the possibility of greater efficacy than previous formulations of LE.

For practitioners, the ability to deliver a suspension drop formulation that requires no shaking, contains a lower concentration of preservative and has a pH level that is more compatible with human tears is certainly a nice addition to our patient care toolkit. RCCL

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(continued from **Editorial,** *pg. 6)*

contact lens solutions in case (4.54).[2]
- Recent contact lens wear (3.22).[2]
- Storing contact lenses in water (5.37).[2]
- Handling contact lenses with wet hands (2.17).[2]

Coupled with the valuable data obtained from previous studies, practitioners can help prevent infection by identifying additional risks and encouraging their patients to engage in recommended hygienic practices.[1,2]

High-risk behavior includes:
- Showering while wearing lenses more than five times a month (9.07).[1,5]
- Reusing solution (3.17).[5]
- Failing to rub lenses at least 10 times per month (9.05).[5]
- Failing to replace lens storage cases every three months (2.79).[5]

Concerted efforts to prevent this dreaded disease are critical. Reducing the number of cases of *Acanthamoeba* keratitis is dependent on practitioners having a better understanding of the disease process, consistently educating patients on the risks and reducing overall exposure. Continued research will help us further understand the disease process and help shape prevention efforts. In the meantime, our best defense is to actively and consistently educate our patients.

The stakes are high. The public has a low tolerance for rare conditions, and patients are counting on you to teach them how to avoid risky contact lens care practices. As a practitioner, the best thing you can do is pay close attention to your patients and don't hesitate to provide gentle reminders. RCCL

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By Mile Brujic, O.D., and Jason Miller, O.D., M.B.A.

From Research to Innovation

Staying tuned in to new developments in contact lens research and technology will enable practitioners to give patients the best of tomorrow's technology.

In health care, research is critical to the growth and acceptance of novel materials, treatments and specific protocols. New breakthroughs within the contact lens field may change your approach as an eye care practitioner, including the way you fit a particular group of patients or how you use a specific medical device. Research drives innovative ideas and development.

There are individuals and companies currently looking to develop new contact lenses with enhanced wetting capabilities, lenses infused with pharmaceutical agents, improved multifocal designs, improved ocular health and lenses that can even alter or shape the developing eye. This month, we look at a few innovative products that hold great promise for our contact lens practices.

Pediatric Lenses

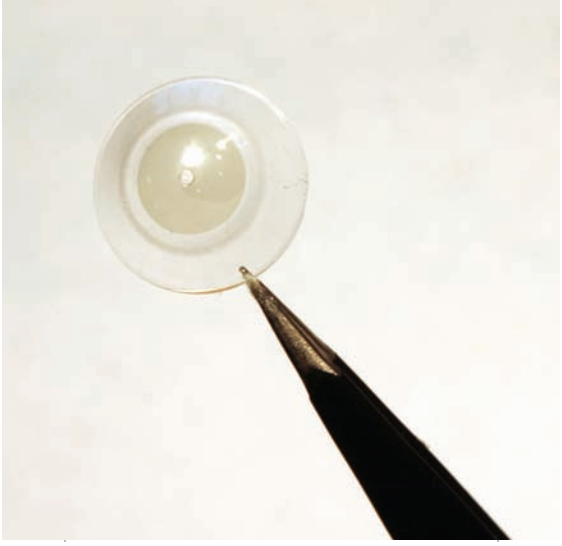
Because fitting children in contact lenses can be challenging, this population is often overlooked. The biggest concern surrounds the child's maturity and ability to take on the responsibility of maintenance and care. Other practitioners worry about the child's interest and motivation to wear contact lenses. A final consideration is the child's personal hygiene habits and ability to take care of the contact lenses without help.[1]

From an ocular health standpoint, the Contact Lenses in Pediatrics (CLIP) study revealed that there were no differences in the biomicroscopic findings between children and teenagers who wore contact lenses.[2] The CLIP study also found that children were as responsible as teenagers in the obligations of contact lens wear.[2]

Today, however, a growing number of eye care professionals are changing their mindset and fitting more children; this new trend largely can be attributed to the availability of new, innovative daily disposable lenses, improved contact lens materials and recent research demonstrating improved performance in activities and sports.[1] Because daily disposables are considered the most convenient to wear and care for, they are often the lens of choice for this population. In fact, a snapshot of the U.S. market over the past few years shows that daily disposable lenses accounted for the most growth within the industry and are expected to continue in that direction.[3,4]

When discussing contact lenses with the child and parents, make sure to explain why you are fitting a specific modality, and underscore the importance of compliance. Take the time to write out your suggested contact care techniques, because we know:[5]

- Three in five contact lens wearers do not wash their hands prior to handling the lenses.
- One in five people do not use fresh solution every time they store their lenses.
- Two in five people have put their contact lenses in their mouth to clean them.
- Seven in 10 contact lens wearers admit to wearing their lenses while swimming.



1. Scientists are designing contact lenses that can help enhance normal vision through 3D panoramic images.[7]

Myopia Control

There has been much research in the area of myopia control, which quickly is emerging as an area of specialty with untapped potential. At the heart of this field of research is this question: "How much reduction in myopia would change your prescribing habits?"

Is it a 25% reduction, 40%, 60% or greater than 80% reduction that would cause you to change your prescribing habit? Personally, if we could tell parents that a 50% reduction in their child's vision impairment is possible, that seems like a significant number. Or, imagine reducing an "expected" -5.00D myope down to a -2.50D myope through a specific treatment interruption that could slow down predicted axial length elongation.

What is causing an increasing prevalence of myopia? Is it nature or nurture? Several researchers are evaluating the role of genetic predisposition, amount of near work, lag of accommodation, levels of vitamin D and even the amount of time spent outdoors in relation to myopia.

New theories, treatments and specific contact lens designs are being formulated with the goal of aggressively halting accelerated axial length growth associated with myopia development.

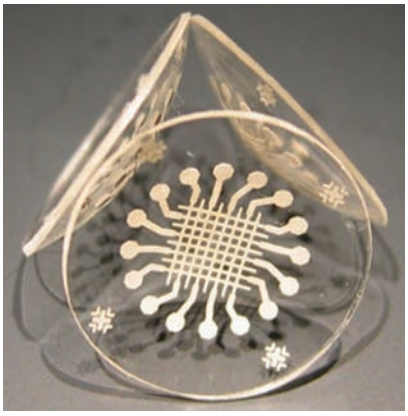
These treatments include progressive addition lenses, light-filtering spectacle lenses, soft contact lenses in all materials, rigid gas-permeable contact lenses (standard fit), soft or rigid bifocal or multifocal contact lenses, orthokeratology lenses, pharmaceutical agents (atropine, pirenzepine, 7-methylxanthine) or vision therapy. They are designed to work on various anatomical areas that influence the refractive state—including the anterior and posterior corneal curvature, corneal thickness, anterior chamber depth, ciliary muscle, axial length of the eye and the accommodation/convergence mechanism.

Alternative Uses of Contact Lenses

Researchers currently are investigating ways to produce a contact lens that automatically adjusts its focus depending on the distance. They potentially could use an "electro-active" element layer attached to the contact lens to restore a perfect focus at all distances. Other projects have looked at developing an electronic circuit on a contact lens that could provide virtual displays, including the Internet and GPS via Wi-Fi-enabled lenses.

New research is looking to treat ocular diseases with the use of "smart" contact lenses that could measure pressure within the eye and dispense medication accordingly (*see "A Blueprint of Tomorrow's Smart Lens," October 2012*). These drug-infused contact lenses could be used for the delivery of many different medications. For example, scientists already have developed a contact lens that releases anesthesia to the eye for post-surgery pain relief; these lenses may soon be part of the treatment protocol for our postoperative PRK patients.[6]

Practitioners today are able to choose from a wide variety of new contact lens materials, lens care solutions, moisturizing eye drops and prescription therapies to improve ocular health. Innovative products and research will continue to drive the market and stimulate growth in areas we may not have considered previously. We recommend that you, as an eye care practitioner, stay current with ongoing research so you can provide the most up-to-date lens care to your patients. RCCL



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By Jason Jedlicka, O.D.

The Astigmatic Ortho-K Patient

Better technology and lens designs allow orthokeratology systems to reshape corneal toricity.

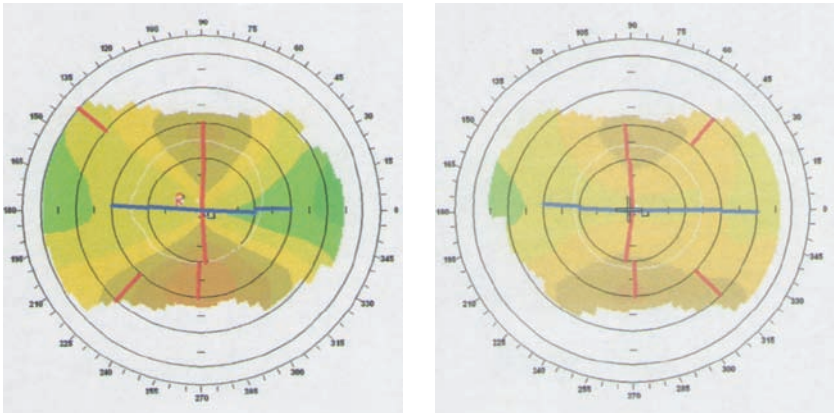
Traditionally, astigmatism has been a challenge to correct with corneal reshaping or orthokeratology lenses. Reports from the early days of FDA-approved corneal reshaping indicate that astigmatism did not improve, or actually worsened, with corneal reshaping.[1] Keep in mind that, a decade ago, the goal of orthokeratology was simply to correct myopia without increasing astigmatism.

Today's manufacturing technology and lens designs have made correcting astigmatism far more possible than in past years. Designs that incorporate toricity into the reverse and landing curves allow lenses to maintain a central position, even on a moderately toric cornea. When this occurs, the spherical base curve is able to reshape much—if not all—of the corneal astigmatism.

A Case Study

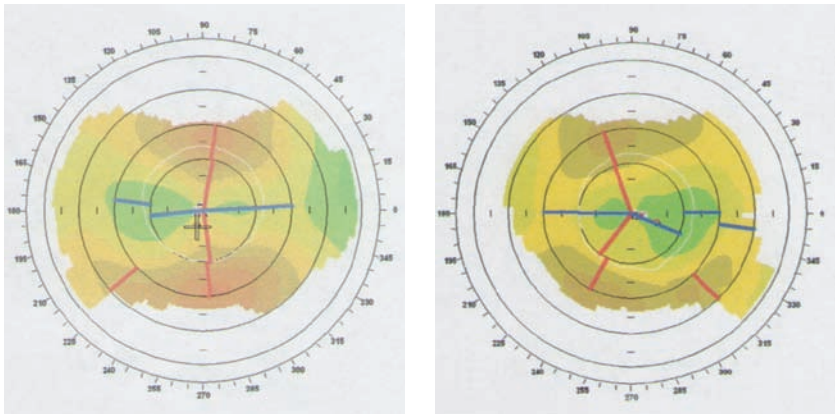
DS, a 54-year-old white female, recently accompanied her 18-year-old daughter for an eye exam. At that appointment, we discussed orthokeratology to correct her daughter's -3.00D myopic prescription. They agreed, and her daughter reported an excellent outcome.

A few weeks later, DS came in for her own eye exam. She was a gas-permeable (GP) lens wearer and used monovision correction in her right eye for near. She mentioned that her daughter was quite pleased with her vision and the orthokeratology lenses, and she was interested in this corrective option for herself. We completed her physical exam, and found a manifest refraction of -4.25 +2.75D x 77 O.D. and -3.25 +1.25D x 105 O.S., and a +2.00D add O.U. Corneal topography revealed a with-the-rule astigmatic cornea (*figure 1*).



1. Pre-corneal reshaping topography O.D. (left) and pre-corneal reshaping topography O.S. (right).

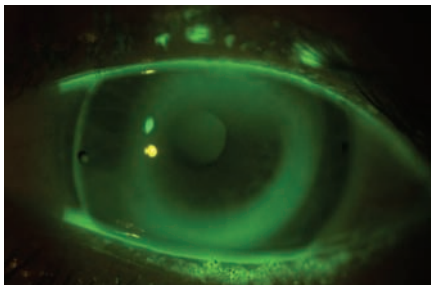
My initial impression was that she was not a particularly good candidate for orthokeratology due to the amount of astigmatism, particularly in the right eye. However, because of her daughter's success, she was quite adamant about trying the modality. After a lengthy counsel about the possibility of a suboptimal outcome, I gave in and agreed to order her a pair of lenses for corneal reshaping. Our goal was to correct the right eye for reading and the left eye for distance. In my experience, switching from GP to orthokeratology lenses is less successful than coming out of glasses or soft lenses. Because she currently was in GP lenses, I asked her to discontinue lens wear for two weeks before returning for lens dispensing.



2. Post-corneal reshaping topography O.D. (left) and post-corneal reshaping topography O.S. (right).

We ordered a pair of lenses with the following parameters: 7.85 base curve, +0.75 add, 10.6mm diameter, 6.0 optic zone and toric peripheral curves O.D., and 7.95 base curve, +0.75 add, 10.6mm diameter, 6.0 optic zone and toric peripheral curves O.S., which were dispensed two weeks later. The initial lenses were marginally tight, so we modified the peripheral curves and reordered O.U. The new lenses were dispensed and worn for a week, at which time DS returned for follow-up. She reported that she was very pleased with her current vision and her tolerance of the overnight lenses. Her visual acuity in the right eye was 20/30 at near with a -1.75 +0.75D x 80 distance correction, while the left eye was 20/15 with no refraction. Additionally, a corneal topography scan revealed flattening of the astigmatism O.U. (*figure 2*). Note the spherical appearance of the lens fit on the right eye (*figure 3*).

Many manufacturers now produce orthokeratology lenses with toric peripheral systems. When an individual has a known degree of corneal astigmatism prior to treatment or when a current lens wearer shows signs of poor centration, moving to a dual-axis or toric design can be helpful. By fully contouring the cornea in the fit zones of the lens, you will find that it stays in a centered position—as opposed to riding above or below the corneal astigmatic ridge. RCCL



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By David L. Kading, O.D., and Mile Brujic, O.D.

OPTI-FREE® PureMoist® MPDS Can Benefit Both Patient and Practice

Keeping our patients comfortable in their contact lenses can have a big impact on overall satisfaction. In this column, we will review how OPTI-FREE® PureMoist® Multi-Purpose Disinfecting Solution can benefit your patients and your practice.

As we previously mentioned, 67% of lens wearers in the United States use silicone hydrogel lenses, which have been shown to reduce on-eye wettability in some cases.[1,2]

OPTI-FREE® PureMoist® MPDS

OPTI-FREE® PureMoist® MPDS helps contact lenses retain moisture through its HydraGlyde® Moisture Matix technology, a unique diblock copolymer (called EOBO) that features two very unique components. One portion of the molecule binds firmly to contact lenses, while the other portion of the molecule attracts moisture. This allows the anchoring of moisture to the surface of the lens, which provides comfort from morning to night.[3-5]

We are constantly on the quest for new ways to enhance the comfort of our contact lens-wearing patients. A recent study followed nearly 600 symptomatic patients who wore one of the four most commonly prescribed silicone hydrogel lenses (Acuvue Oasys* [Vistakon], AIR OPTIX®AQUA† [Alcon], Biofinity* [CooperVision] or PureVision*[Bausch + Lomb]) and utilized OPTI-FREE® PureMoist® MPDS solution.[6] The results found a dramatically positive effect in the patients' wearing experience. Following 30 days of lens wear utilizing OPTI-FREE® PureMoist® MPDS, these patients were able to comfortably wear their lenses for nearly two hours.

The study also found an improvement in the patients' overall comfort. Although the study wasn't designed to look at contact lens dropout rates, the authors said, "It is possible that an improvement in perceived comfort may help reduce the dropout rate in the population of subjects who often experience discomfort with contact lens wear."[6]

This type of lens-wearing improvement can have a substantial effect on the patients' daily routine and overall quality of life.

The Financial Bottom Line

Keep in mind that patients who remain in contact lenses are significantly more profitable for your practice. Over the course of six years, contact lens wearers generate 91% more revenue than patients who only wear glasses.[7] In one simulation, a glasses-only patient generated $878 worth of revenue for the office, compared to $1,678 generated by the contact lens-wearing counterpart.[7]

Mile Brujic, O.D., and Jason Miller, O.D., M.B.A., described two practices with 1,000 contact lens patients. One practice worked hard to keep its patients wearing contact lenses, while the other watched its contact lens patient population diminish due to complacency. After six years, the difference between these two practices in accumulated revenue totaled $600,000.[8]

Therefore, we need to go above and beyond to guarantee their patients stay in contact lenses. One easy way to do so is by recommending OPTI-FREE® PureMoist® MPDS to your patients. In a 2011 survey, 94% of practitioners said they recommend a specific solution to their patient.[1]

A strong solution recommendation that resonates with our patients can increase the comfortable wear experience for nearly two hours per day. Prescribing OPTI-FREE® PureMoist® MPDS will help improve your patients' comfortable lens-wearing experience, and ultimately create happy patients and ambassadors for your practice.

Better patient outcomes produce loyal patients. Loyal patients tend to make strong recommendations to their friends and family. This can have a substantial impact on your practice's patient load and subsequent revenue.

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†AIR OPTIX® AQUA (lotrafilcon B) contact lenses: High oxygen transmissible lenses. Dk/t = 138 @ -3.00D.
Important information for AIR OPTIX® AQUA (lotrafilcon B) contact lenses: For daily wear or extended wear up to 6 nights for near/far-sightedness. Risk of serious eye problems (i.e., corneal ulcer) is greater for extended wear. In rare cases,loss of vision may result. Side effects like discomfort, mild burning or stinging may occur.
See product instructions for complete wear, care, and safety information.

A Wide-Angle View of Keratoconus

To treat keratoconus effectively, today's eye care practitioners must understand the disease better. Here, a surgeon reviews its causes and remedies.

By Thomas John, M.D.

Keratoconus, and its siblings—pellucid marginal degeneration, keratoglobus and posterior keratoconus—collectively make up the family of non-inflammatory corneal thinning diseases (NICTD). As in any family, each member may look slightly different. For example, NICTD can be diffuse as in keratoglobus, or more focal as in keratoconus, pellucid marginal degeneration and posterior keratoconus.

Any deviation from the normal corneal contour and physical structure has a degrading effect on the patient's best-corrected visual acuity. In some cases, visual quality can be so adversely affected as to warrant surgical intervention. Such corneal shape and structural alterations also adversely change its biomechanical properties; additionally, corneal thinning can make the individual more susceptible to traumatic ocular injury. In fact, in brittle cornea syndrome—which is comprised of keratoconus or keratoglobus, blue sclera, skin hyperelasticity and joint hypermobility—minor trauma can precipitate corneal rupture.[1]

We have a global responsibility to continue advancing research to ultimately unravel the etiological mysteries of keratoconus. In doing

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so, we may be able to correct the disease at its origin, treat the individual to improve vision and protect the worldwide population from advanced corneal thinning.

Understanding Keratoconus

The cone-shaped corneal protrusion we have come to call keratoconus affects all races, both sexes evenly and has a mean age of onset at 16 years. The true incidence is unknown, though large studies estimate 50 to 230 cases per 100,000 people in the general population.[2] One study estimated the prevalence in first-degree relatives to be 3.34%, which is 15 to 67 times higher than general population (0.23% to 0.05%).[3]

The etiopathogenesis of keratoconus remains a mystery for the most part. Because keratoconus is non-inflammatory, genetics need to be investigated. Interestingly, just fewer than 10% of cases are believed to be of familial origin.[4]

The application of newer technology, such as Orbscan II (Orbtek/Bausch + Lomb), has bumped up this number to 25% by including relatives of keratoconus with one or more keratoconus traits, as compared to 1% in the control group with relatives who showed a single keratoconus trait.[5] The parameters and abnormality thresholds include: keratometry (≥47.2D), I-S value (≥1.2D), posterior float apex (≥42µm) and thinnest pachymetry (≤463µm).[5] Mapping studies revealed multiple loci for autosomal dominant keratoconus, including 16q22.3-q23, 5q14.3-q21.1 and others, which displayed genetic heterogeneity.[6,7]

From a genetic perspective, keratoconus seems to have an autosomal dominant pattern of inheritance with variable expressivity. In addition, other causative associations include mechanical eye rubbing (which may be linked to epithelial trauma), activating wound-healing mechanisms and signaling pathways in addition to its direct effect on keratocytes.[8] Contact lens wear also contributes to mechanical epithelial trauma. While the distribution of corneal collagen is shown in Table 1, biochemical studies seem to indicate that the role of proteolytic enzyme digestion and the involvement of interleukin-1 (IL-1) are possible causative factors in some cases of keratoconus.[2]

Table 1. Corneal Collagen Distribution

Number	Layer	Collagen Type
1	Epithelium	IV, VII
2	Bowman's Layer	V
3	Stroma	I, III, V, VI
4	Descemet's Membrane	IV, VIII
5	Endothelium	None

Presentation

The most prominent symptom of keratoconus is bilateral, often asymmetric, progressive, blurred and distorted vision, due to a combination of myopia and astigmatism presenting often in the teenage years. The condition is rarely seen after age 40. While progression may last 10 to 20 years, it may stop at any time, from mild to advanced stages.

Complaints such as glare, monocular diplopia, polyopia and photophobia are common. There also may be associated eyestrain and fatigue.

The broad spectrum of keratoconic findings include corneal ectasia in the form of a cone with corneal thinning and steepening, intraepithelial iron deposition at the cone base (Fleischer ring) and lower eyelid protrusion and angulation on down gaze (Munson's sign). Also look for posterior, deep stromal and Descemet's membrane vertical lines that parallel the cone axis called Vogt's striae; these lines may temporarily vanish on digital pressure. Other findings include ophthalmoscopic oil droplet reflex in a dilated fundus exam ("Charleaux"), retinoscopic scissoring reflex and Rizutti's sign in advanced keratoconus, which consists of a sharply focused light beam temporal to the nasal limbus when the cornea is laterally illuminated.

Corneal nerves may be prominent. Corneal hydrops or previous contact lens wear can result in corneal scarring. Sudden visual compromise may be secondary to corneal hydrops due to the focal Descemet's membrane break, which usually results in scar formation. Histologic alterations can affect the epithelium, Bowman's layer, stroma and Descemet's membrane in corneal hydrops, while the endothelium is usually normal. Cone types include nipple (central location) and oval or sagging cones that are located inferiorly or inferotemporally. The cone type or shape does not contribute any insight to the etiology of keratoconus. Management decisions, especially surgical, will depend solely on how long the patient is able to wear a contact lens during the day to meet his/her daily activity requirements.

From a clinical viewpoint, keratoconus has been associated with vernal keratoconjunctivitis, floppy eyelid syndrome, posterior polymorphous corneal dystrophy, Leber's congenital amaurosis, retinitis pigmentosa and other diseases.[9-13] Systemic associations of keratoconus include atopy

(asthma, hayfever and eczema), connective tissue ailments (i.e., osteogenesis imperfecta), and Ehlers-Danlos, Down's and Turner syndromes.[14-18] The CLEK study looked at 1,209 patients with keratoconus and found that corneal scarring contributed to a decrease in high- and low-contrast visual acuity in these patients.[19]

Although there are many singular reports of coexistence with other disorders, it is important to note that the most frequent keratoconus presentation is sporadic and isolated without any link to ocular or systemic disease that can be detected clinically.[2] A cardiac evaluation may be advised, particularly in advanced keratoconus cases, due to its known association with mitral valve prolapse.

Diagnosis

The degree of keratoconus may be based on corneal curvature and corneal thickness (*see Table 2, page 18*). Forme fruste or subclinical keratoconus indicates that the cornea is at risk for developing keratoconus over time, and is diagnosed based on videokeratography alone and without any clear clinical signs of keratoconus. This condition is suspected based on three indications:

- A central keratometry >47D.
- An oblique astigmatism >1.5D.
- Videokeratographic superior-inferior curvature disparity of >1.4D.

In the normal peripheral cornea, collagen lamellae run circumferentially, which contributes to a round shape. But when there is stromal thinning as in cases of keratoconus, it results in corneal curvature flattening along that meridian, which induces a more oval shape to the peripheral collagen lamellae. This ovalization is associated with secondary transmission of compressive force to the collagen lamellae 90° apart, which results in the steepening of that meridian, called a biomechanical coupling effect. In addition, the IOP causes outward pushing of the cornea at the site of corneal weakening. This is partly the basis of corneal imaging alterations seen in keratoconus and some of the other corneal contour changing disease entities.

With newer therapeutic modalities hitting the market, early detection and prevention of keratoconus is of paramount interest. First, we need to detect pre-slit-lamp manifestations of keratoconus. Since the Swiss ophthalmologist Marc Amsler's application of the photographic Placido disc in 1938 to elicit early topographical alterations in keratoconus prior to clinical detection, we have seen several new technologies. These include photokeratoscopy (topography), computer-assisted videokeratoscopy, scanning slit topography (e.g., Orbscan) and, most recently, the Pentacam (Oculus), which uses a rotating Scheimpflug camera to assess the cornea.[2]

The advantages of Pentacam include coverage of the central cornea, the ability to measure severe corneal irregularities that may not be possible with Placido imaging, and limbus-to-limbus pachymetry. Four important videokeratographic indices for keratoconus screening include central corneal power >47.2D, Sim-K astigmatism >1.5D, inferior-superior dioptric asymmetry >1.2D and skewed radial axes >21°.[20]

OCT may be supplemental, and will help identify the areas of corneal thinning.

Treatment

To treat keratoconus, use a step-ladder approach: glasses, followed by contact lenses and, if these treatments fail, surgery. In the past, penetrating keratoplasty was the go-to surgical choice. Today, we can choose from a treatment matrix. Procedure choice may be influenced by the surgeon's comfort level in performing newer surgical techniques, patient expectation, the request for newer procedures and the need for postoperative speed of visual recovery, not to mention insurance coverage constraints.

Consider endothelial retention procedures to eliminate postsurgical endothelial graft rejection by lamellar procedures such as deep anterior lamellar keratoplasty (DALK), total anterior lamellar keratoplasty (TALK) or hemi-automated lamellar keratoplasty (HALK). Additional choices include corneal inserts, phakic IOLs and full-thickness penetrating keratoplasty.

Intacs corneal implants are a reversible procedure that opens up an intermediary stage, or stop-gap procedure, prior to corneal transplantation. While the effects of Intacs on natural disease progression are not yet fully understood, this procedure may be beneficial in some moderate cases of keratoconus with an absence of corneal scarring. Another corneal insert, Ferrara rings, is not FDA-approved for use in the United States.

Rather than a corneal procedure, you may also want to consider an intraocular treatment and the use of phakic IOLs. Phakic IOLs may be a consideration in correcting myopia and compound myopic astigmatism, especially in keratoconus that has been stable with a relatively good best-corrected visual acuity and absence of any central corneal scar. In cases of clinically documented keratoconus progression, one may consider newer technology such as collagen cross-linking first,

followed by phakic IOLs after a stable cornea has been established.

This brings us to the use of collagen cross-linking with riboflavin, which can stabilize keratoconus and prevent progression. However, we are still awaiting results from continued multi-year studies to provide answers on its long-term efficacy and safety as a treatment modality. Recent studies indicate keratocyte loss in anterior and mid-stroma, both in the central and peripheral cornea, after cross-linking in human keratoconus.[21]

What is the role of refractive surgery in keratoconus? Remember that LASIK is contraindicated in established keratoconus. Similarly, because the cornea is thinner than normal and is considered biomechanically weak, one may avoid removing anterior corneal tissue that may accelerate keratoconus, such as in cases of PRK.

What is debatable, however, is whether forme fruste keratoconus should be placed in the same class as established keratoconus. If appropriate, consider surface ablation in selective cases to possibly relieve the patient of difficult contact lens wear. Forme fruste keratoconus patients with stable corneal imaging over time and sufficient corneal stromal thickness may be candidates for such treatment options. In fact, to not offer such treatment may be on the extreme side of a conservative approach. There is no consistent evidence to indicate that, in the long term, surface ablation of forme fruste keratoconus accelerates the condition to overt keratoconus.

Table 2. Keratoconus Grading.

Description	Mild keratoconus	Moderate keratoconus	Advanced keratoconus
Corneal curvature	<45D	45D - 52D	52D - 65D (Severe >62D)
Corneal thickness (microns)	506µm (Normal 543µm)	473µm	446µm

Most importantly, the patient and surgeon need to enter collectively into a detailed dialogue to discuss these options and make a unanimous decision.

Keratoconus is a condition that intrigues and challenges the treating physician in the ultimate quest to improve your patient's visual homeostasis and quality of life. Familiarity with corneal imaging technology, combined with a clinical skill set that is focused on early detection and treatment, is essential for success. With a continued effort from both the research and clinical sectors, hopefully we can prevent or curtail keratoconus in future generations. RCCL

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CE TEST FOR A WIDE-ANGLE VIEW OF KERATOCONUS

1. Which diseases are considered non-inflammatory corneal thinning diseases (NICTD)?
a. Keratoconus.
b. Pellucid marginal degeneration.
c. Keratoglobus.
d. All of the above.

2. What is the mean onset age of keratoconus?
a. 16 years.
b. 63 years.
c. 25 years.
d. 42 years.

3. What percentage of keratoconus cases is considered hereditary?
a. 5% to 8%.
b. 50% to 55%.
c. 33% to 40%.
d. 10% to 25%.

4. What is one of the most prominent symptoms of keratoconus?
a. Double vision.
b. Color blindness.
c. Blurred vision.
d. Headaches.

5. Which is NOT a common keratoconic finding?
a. Focal corneal thinning and steepening.
b. Intraepithelial iron deposits.
c. Retinoscopic scissoring reflex.
d. Uniform corneal thinning of entire cornea.

6. What other diseases may be associated with keratoconus?
a. Floppy eye syndrome.
b. Posterior polymorphous corneal dystrophy.
c. Leber's congenital amaurosis.
d. All of the above.

7. What is NOT an indication of keratoconus?
a. A central keratometry >47D.
b. Kayser-Fleischer ring.
c. Videokeratographic superior-inferior curvature disparity of >1.4D.
d. An oblique astigmatism >1.5D.

8. What is NOT helpful in diagnosing keratoconus?
a. Confocal microscopy.
b. Computer-assisted videokeratoscopy.
c. Photokeratoscopy.
d. Scanning slit topography.

9. What are the advantages of the Pentacam (Oculus)?
a. Coverage of the central cornea and the ability to measure severe corneal irregularities.
b. A rotating Scheimpflug camera obtains optical corneal cross sections.
c. Reliably measures both the anterior and posterior corneal surfaces.
d. All of the above.

10. What is an important videokeratographic indice for keratoconus?
a. Sim-K astigmatism >1.5D.
b. Inferior-superior dioptric asymmetry >1.2D.
c. Skewed radial axes >21°.
d. All of the above.

Examination Answer Sheet

Valid for credit through November 1, 2015

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Rate the effectiveness of how well the activity:

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Signature _____ Date _____

Lesson 108692 RO-RCCL-1112

A Closer Look at Corneal Inflammation

Inflammatory events often appear to be similar. This guide will help you make the proper differential diagnosis and select an appropriate treatment.

By Mark McKenzie, O.D., and Walt Whitley, O.D., M.B.A.

Dr. McKenzie is a resident at the Louis Stokes Cleveland VA Medical Center.

Dr. Whitley is the director of optometric services at Virginia Eye Consultants in Norfolk, Va.

Eye care practitioners see a variety of anterior segment diseases and disorders with similar presentations. In cases of red eyes, clinicians must determine whether the inflammatory event is sterile or infectious in nature, and then determine the appropriate course of treatment. In this article, we will review corneal inflammatory events and considerations for clinical care.

What is Inflammation?

Inflammation stems from the body's active or reactive methods of protecting tissues and organs. It is an efficient, non-specific response caused by injury, infection, autoimmune processes or idiopathic conditions. During this process, the body's white blood cells and other immune factors protect against foreign pathogens such as bacteria and viruses. In certain conditions the body becomes symptomatic, subjecting the patient to redness, warmth, swelling and pain.

Episodes can present as acute (hours to days) or chronic (weeks to years) with varying severities. Our goal is to aggressively treat acute inflammatory events and prevent chronic inflammation from damaging the ocular tissues, possibly leading to blindness.

Pathophysiology

The inflammatory response differs in vascular and avascular tissue.

In vascular tissues, inflammation is an asset that helps defend the body. Vasodilation leads to redness and an increase in size of the blood vessels. There is an increase in vascular permeability, which allows fluid to get into the affected area. Thereafter, white

blood cells migrate into the tissue to fulfill their role and attempt to remove the offending agent.

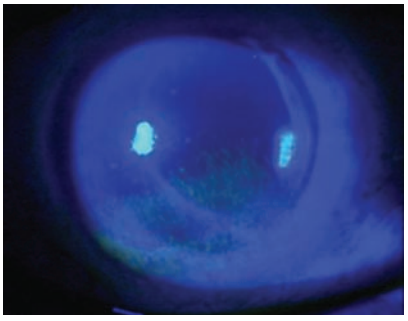
In avascular tissues, inflammation is a liability that can lead to tissue damage and scarring. The normal cornea is transparent and maintains itself as an immune privileged site, in part because it is avascular. For the cornea, the response of the limbal vasculature accounts for vessel penetration and infiltrative events.[1] If not adequately treated, chronic inflammation can lead to fibrinization secondary to inflammatory cells, granulomatous formation, deposition of fibroblasts, tissue hardening and destruction, neovascularization and pannus.[2]

In its natural state, the cornea is 78% water. Any significant increase in water content can lead to corneal edema and a loss of transparency.[3] The cornea is surrounded by fluid on both sides—tear film anteriorly and aqueous posteriorly. Both the corneal epithelium and endothelium act as barriers to control the amount of fluid that is allowed to move into the tissue.

Superficial squamous cells of the epithelium are surrounded by a continuous band of tight junctions that prevent fluid from entering the stroma. Endothelial cells allow fluid to move between the cornea and the anterior chamber, but this movement is controlled by transport proteins in the cell membrane that regulate the osmotic gradient between the stroma and the aqueous.[5]

Signs

A host of slit-lamp findings may appear in response to corneal inflammatory events. Distinguishing among them can yield important clues to the cause and can help to guide treatment decisions.



1. Superficial punctate keratitis.

• ***Superficial punctate keratitis (SPK).*** The most common sign of corneal inflammation, SPK can be caused by and associated with numerous ocular conditions, most commonly dry eye disease (*figure 1*). According to Ashley Behrens, M.D., and colleagues, superficial punctate keratitis is a common finding in patients who present with Level 2 dry eye disease.[6] Additional signs of corneal inflammation include corneal swelling (epithelial or stromal edema), abnormal vessel growth (pannus and neovascularization), corneal infiltrates (accumulation of inflammatory WBCs), corneal ulceration and immune-mediated inflammation.

• ***Punctate epithelial erosions (PEE).*** A non-specific finding that appears clinically as tiny defects in the epithelium that stain with fluorescein, PEE are an early sign indicating epithelial compromise and are associated with many pathologic inflammatory conditions.

• ***Punctate epithelial keratitis (PEK).*** PEK appears as areas of focal, intraepithelial infiltrates, associated with areas of punctate staining.[7]

• ***Subepithelial infiltrates (SEI).*** SEIs generally occur after viral keratitis, but are also found in blepharitis and contact lens-related hypersensitivity. They result when chemical-signaling molecules draw white blood cells from the limbal vasculature into the avascular cornea.

• ***Corneal swelling.*** This may occur in different layers of the cornea; the type of swelling can be differentiated based on clinical appearance. Epithelial edema can present as epithelial microcysts, microcystic edema or epithelial bullae.

Epithelial microcysts are small, round, refractile lesions that originate in the basal layers of the epithelium and migrate toward the surface, where they stain with fluorescein.

Bullae form when excess fluid accumulates in the corneal epithelium, causing the surface epithelial layers to separate from the basement membrane. They appear as flat, pebble-like lesions and can present in a variety of configurations.[3]

Swelling of the corneal stroma manifests as an increase in stromal thickness. The appearance of edema in this region varies from a mild granular haze to a dense gray opacity and may produce folds in Descemet's membrane if severe. Stromal edema may occur in response to compromised epithelial or endothelial cells.

• ***Neovascularization and pannus.*** Normally, the cornea is an avascular structure; however, neovascularization and pannus may occur in response to inflammatory disease.

Neovascularization can be caused by hypoxic conditions created by contact lens overwear, or it can form in response to inflammation from interstitial keratitis, viral keratitis or chemical burns.[3]

Pannus is a proliferation of fibrovascular tissue from the limbus that extends onto the cornea and is seen in conditions such as trachoma and superior limbic keratoconjunctivitis.[3]

Common Causes

• ***Immune-mediated corneal inflammation.*** One common cause

Is it Infectious or Sterile Inflammation?

Infectious Ulcer: pain, single lesion, >2mm, AC reaction.
Sterile Infiltrate: minimal pain, multiple lesions, <2mm, none to minimal AC reaction.

of corneal inflammation is an abnormal response from the host's immune system. This can be the result of a hypersensitivity reaction to non-pathologic bacterial byproducts or by autoimmune disease directed at host tissue.[8]

Sterile keratitis is an inflammatory reaction to bacterial byproducts without direct corneal infection in contact lens wearers and lid margin disease. Bacteria colonize the contact lens surface producing toxins, which can be the catalyst for infiltrative keratitis. Hypersensitivity to contact lens solution can also occur.[4] By a similar mechanism, colonization of the eyelids can cause phlyctenular keratoconjunctivitis or marginal keratitis.

Additionally, the host's autoimmune system can be directed at the corneal tissue itself, as is believed to be the case in Mooren's ulcer.[3]

• ***Infectious keratitis***. Microbial keratitis is a major source of corneal inflammation and can be caused by bacterial, viral, fungal or parasitic invasion.

In response to bacterial infection, chemical-signaling molecules such as tumor necrosis factor-alpha and interleukin-1 cause neutrophils to escape the limbal blood vessels and move to the site of infection. Eventually macrophages arrive to phagocytize bacteria and degenerated neutrophils.[3] The type of chemical mediators and immunologic cells involved depend on the source of the infection. Clinical signs of bacterial keratitis include corneal ulceration with stromal infiltration, corneal edema, anterior uveitis, hypopyon and perforation.[7]

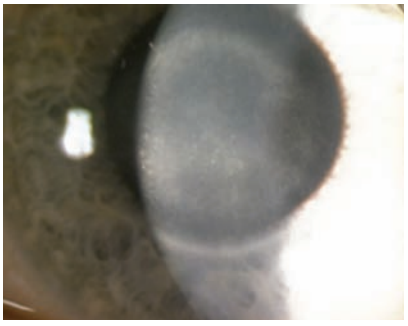
The most common forms of viral keratitis are herpes simplex (HSV) and herpes zoster keratitis (HZO). HSV comes in several forms, including epithelial keratitis, neurotrophic keratitis, necrotizing stromal keratitis and endotheliitis:[3]

Epithelial keratitis is characterized by punctate or stellate epithelial lesions that progress to dendritic ulceration with characteristic terminal end-bulbs. The bed of the ulcers stain well with fluorescein and the margin stains with rose bengal. If not treated properly, lesions may progress to geographic ulceration.

Neurotrophic keratitis is characterized by a non-healing epithelial lesion with a gray, opaque stroma underneath, which may become thinned.

Necrotizing and non-necrotizing stromal keratitis presents with stromal necrosis, anterior uveitis and keratic precipitates.[7] The inflammation present in HSV stromal keratitis is a hypersensitivity reaction to viral antigen (*figure 2*). Endotheliitis invariably displays keratic precipitates, stromal and epithelial edema, and iritis.[3]

As compared with HSV keratitis, herpes zoster keratitis includes epithelial keratitis—characterized by small, non-ulcerated, pseudodendritic lesions without terminal bulbs. Other presentations of viral keratitis include nummular keratitis, which presents with sub-epithelial infiltrates and stromal haze, disciform endotheliitis and anterior uveitis (*figure 3*).[7]



2. HSV disciform keratitis.

Fungal infections of the cornea typically have a gradual onset of pain and photophobia, and often occur in response to a traumatic injury. The cornea displays an infiltrative grayish/white ulcer and has less distinct, more feathery margins. Other associated findings include satellite lesions, a thick endothelial exudate, anterior uveitis and hypopyon.

Acanthamoeba keratitis is a parasitic infection of corneal tissue. Infiltration along corneal nerves, known as radial keratoneuritis, is pathognomonic for *Acanthamoeba* infection.[7] The hallmark clinical presentation in the early stages of infection is advanced ocular pain out of proportion with signs. Epithelial pseudodendrites, anterior stromal infiltrates and a ring abscess may also be present.

As the *Acanthamoeba* infection progresses, subepithelial infiltrates can develop along corneal nerves with later formation of a ring stromal infiltrate. Patients who typically present with *Acanthamoeba* keratitis are typically contact lens wearers with poor hygiene and/or exposure to freshwater systems, pools and hot tubs.

• ***Endothelial dysfunction***. Any damage to the corneal endothelium can result in corneal edema, because these cells are responsible for regulating the osmotic gradient between the cornea and the anterior chamber. Causes of stromal swelling due to endothelial dysfunction include trauma during intraocular surgery, dystrophies of the corneal endothelium, iritis,

viral keratitis or increased IOP. The most common of these is Fuchs' dystrophy—focal accumulations of abnormal collagen on Descemet's membrane (guttata) where the endothelial cells lose their ability to regulate ion movement.

Viral keratitis can cause direct inflammation of the endothelium, impacting its ability to regulate hydration.[3]

Swelling can also be seen in the presence of a healthy, intact corneal endothelium. With an intraocular pressure of 55mm Hg or greater due to angle closure glaucoma or viral infections (HSV, HZO), hydrostatic pressure from the aqueous becomes too great for the endothelial pumps to overcome and edema forms.[3]

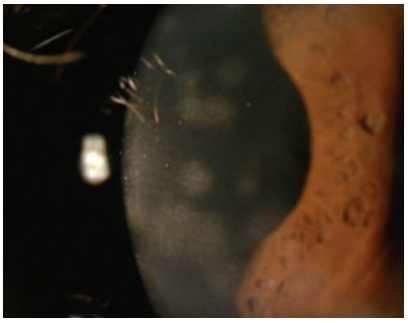
Treatment

Treat corneal inflammation by identifying and targeting the specific underlying etiology. First, distinguish whether the corneal condition is infectious or inflammatory in nature. When in doubt, treat as infectious until proven otherwise. Once the infection is under control, anti-inflammatory drugs can always be added to reduce the risk of haze and scarring.

There are several classes of medications used in treating corneal inflammation, including corticosteroids (alone or in combination), cyclosporine A and hypertonic agents.

Steroids address inflammation in a variety of ways:

1. Steroids inhibit phospholipase A_2, which prevents arachidonic acid from being released. Doing so inhibits the formation of prostaglandins, leukotrienes and lipoxins, which are powerful chemical mediators in the inflammatory cascade.[9]



3. Nummular keratitis.

2. Steroids inhibit pro-inflammatory cytokines, which call on other inflammatory cells to increase phagocytosis.

3. Steroids inhibit the production of complement molecules, which activate mast cells and basophils.

4. Steroids decrease the permeability of the capillary system and decrease fibroblast proliferation, thereby minimizing tissue damage.

There are many topical ocular steroids to choose from, differing in potency, bioavailability and safety. cyclosporine regulates inflammation by inhibiting the T-cell's ability to produce pro-inflammatory signaling molecules. It is commonly used in dry eye syndrome and to prevent corneal graft rejection.

Hyperosmotic agents draw fluid out of the cornea by creating an osmotic gradient between the cornea and tear film. They are often used to improve comfort and vision in cases of bullous keratopathy; however, glycerin can also be used for diagnostic purposes.[10]

The most important consideration when treating corneal inflammation is to follow each patient until resolution. This ensures proper patient management and allows us the ability to monitor the condition and modify the treatment when necessary.

Corneal inflammation is a common finding and co-exists with other conditions of the ocular anatomy. Understanding the common symptoms and the individual clinical signs can better aid the practitioner in making the proper diagnosis.

In avascular structures such as the cornea, prompt treatment and continuous patient management can be key in providing an optically clear ocular surface. RCCL

Commercially Available Steroids

Topical Corticosteroids

Loteprednol etabonate 0.2% ophthalmic suspension
Loteprednol etabonate 0.5% ophthalmic suspension or ointment
Difluprednate 0.05% ophthalmic emulsion
Prednisolone acetate 1% ophthalmic suspension
Prednisolone sodium phosphate 1% solution
Rimexolone 1% ophthalmic suspension
Fluorometholone acetate 0.1% ophthalmic suspension
Fluorometholone alcohol 0.1% suspension or ointment

Combination Antibiotics/Steroids

Neomycin/polymyxin B with dexamethasone
Neomycin/polymyxin B with hydrocortisone
Neomycin/polymyxin B with prednisolone acetate
Gentamycin with prednisolone acetate
Tobramycin with dexamethasone
Tobramycin with loteprednol
Sodium sulfacetamide and prednisolone acetate

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The Antimicrobial Evolution

With several new therapies in the pipeline, practitioners may soon have a new arsenal of drugs to better treat ocular infections.

By Mark B. Abelson, M.D., C.M., Aron Shapiro and Caroline Tobey

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School and senior clinical scientist at the Schepens Eye Research Institute.

Antimicrobials are an exemplary display of therapeutic evolution. The historical medicine cabinet of antimicrobials has been stocked with increasingly efficacious therapies that have been incredibly powerful and fast acting. However, time has not been a friend to this class of drugs. Co-evolving antibacterial resistance is the main enemy, and the current pipeline of antimicrobial therapies must adapt to respond to this omnipresent threat.

In this article, we will discuss clinical research and new antimicrobial therapies in development that show promise in treating today's—and tomorrow's—ocular infections.

The Origin of Species

The problem with any antibacterial medication is that the battle must be fought continuously. An antibiotic may work effectively initially, but over time, ocular microbes can become resistant.

Upon exposure to an antibacterial agent, bacteria that are naturally resistant to a drug have a chance to proliferate preferentially over more susceptible bacteria. We commonly—and incorrectly—believe that bacteria are "developing"increased resistance to a certain drug; in actuality, the proportion of bacterial isolates naturally resistant to that drug is increasing. Remember, bacteria do not become resistant to an antibiotic after exposure. Rather, a genetic mutation in the encoding alters their susceptibility to the drug. Upon exposure to an antibacterial agent, bacteria with these types of natural resistance mutations will be able to reproduce at a quicker rate than the vulnerable bacteria. Over time, the bacterial population shifts to contain a greater proportion of antibacterial-resistant bacteria.

Keep in mind, though, that bacteria can resist drugs through one or more potential mechanisms. Resistance to penicillin and cephalosporins can be achieved by bacterial expression of a beta-lactamase enzyme, which inactivates the molecular structure of the drug. In other cases, mutations of their cell wall receptors reduce or block the drug's ability to bind to the bacteria. Bacteria with mutated DNA gyrase or topoisomerase IV enzymes can evade fluoroquinolone antibacterial actions.[1]

There is a large genetic variation

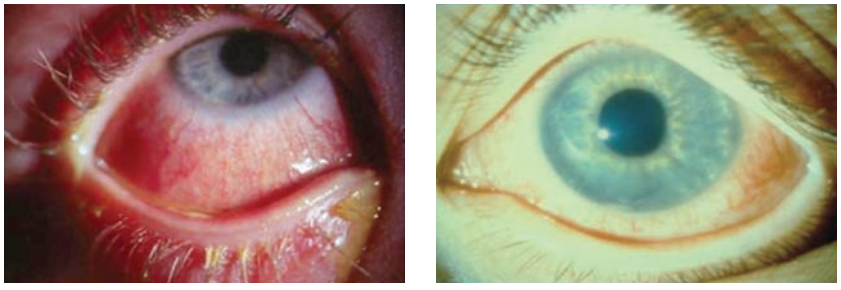
between bacterial species; because of this, it's likely that some bacteria will be naturally resistant to any given antibacterial.

Antibiotics and Beyond

Besides bacterial conjunctivitis and blepharitis, sight-threatening ocular infections (e.g., microbial keratitis and endophthalmitis) are the most serious diseases that antibiotics target. Although many effective ophthalmic antibacterials are available in the United States today, broad-spectrum fluoroquinolones constitute a majority of the market, as they have been shown to be a valuable addition to the anti-infective spectrum. However, they face progressively higher levels of resistance. Susceptibility surveys such as the Ocular TRUST (Tracking Resistance in U.S. Today) longitudinal surveillance study, which examined the *in vitro* antimicrobial susceptibility of ocular isolates collected in the U.S. from 1999 and 2006, revealed an increasing incidence of multidrug-resistant organisms in ocular infections. The study also found that the prevalence of methicillin resistance among the isolates increased from 29.5% in 2000 to 41.6% in 2005.[2]

It has also been reported that methicillin-resistant *Staphylococcus aureus* (MRSA) infections account for 18% of culture-positive cases of endophthalmitis.[3] Moreover, methicillin resistance shares certain links with fluoroquinolone resistance: If a bacterium is methicillin resistant, there is an 85% chance that it will also be resistant to the entire class of fluoroquinolones.[2]

The Antibiotic Resistance in Ocular Microorganisms (ARMOR) surveillance study found a high level of MRSA strains, and the Ocular TRUST study confirmed the high concordance between methicillin resistance and pan-fluoroquinolone resistance in *Staphylococcus aureus* and *Staphylococcus epidermidis*.[1,4]



New innovations in antimicrobial therapy aim to target such as infections bacterial conjunctivitis (left) and viral conjunctivitis (right).

In an effort to combat this resistance concern, promising new drugs in the quinolone family—namely, isothiazoquinolones (ITQs)—are in development and add a third mechanism of action as potent DNA primase inhibitors.[5-10] Fluoroquinolones typically inhibit both DNA gyrase and topoisomerase IV, which are required for the DNA replication process. This new class has been found to have good *in vitro* and *in vivo* activities against several key bacterial pathogens such as *Staphyloccocus aureus*, including MRSA isolates.[5]

ITQs are structurally different from fluoroquinolones, with substitution in the typical 3-carboxyl group by an isothiazolone ring. This modification helps with inhibition of DNA primase, thereby increasing efficacy and decreasing the chances of developing resistance compared with fluoroquinolones. Bacterial DNA primase is essential for DNA replication in gram-positive and gram-negative bacteria, and is also structurally distinct from eukaryotic primases. It represents an attractive target for therapeutic intervention. With that in mind, in a survey designed to acess ocular pathogen prevalence and emerging antibiotic therapy, researchers examined the *in vitro* activity of a novel ITQ, ACH-0139586, against ocular pathogens (*S. aureus*, *S. epidermidis*, *S. pneumoniae*, *H. influenza*, *M. catarrhalis* and *P. aeruginosa*) compared with moxifloxacin and gatifloxacin. The study demonstrated that ACH-0139586 was more potent relative to gatifloxacin and moxifloxacin, regardless of methicillin and fluoroquinolone resistance, and that this was most apparent against evaluated gram-positive pathogens.

ACH-0139586 has a novel target profile against bacterial DNA replication enzymes and potent broad-spectrum bactericidal activity, characteristics that indicate it may play an important role against drug-resistant bacteria.[11] Because of its exciting antibacterial spectrum and positive kill curves, this novel compound shows great promise as a next generation treatment.

The Need for New Antivirals

On the other side of the anti-infective spectrum, advances in antiviral therapy are slowly making their way to the forefront of ocular research and development. Treatment for viral conjunctivitis has typically been limited to symptomatic therapy and epidemiological measures of control in order to reduce transmission; or to topical corticosteroid treatment in order to reduce immune infiltration.[12] A variety of viruses can be responsible for conjunctival infection; however, adenovirus is the most common cause. The competition for the first FDA-approved drug for the treatment of viral conjunctivitis is fierce. Thankfully, an array

of drugs are in the pipeline for this unmet need.

NovaBay has developed an eye drop formulation for the treatment of viral conjunctivitis. NVC-422 uses NovaBay's class of aganocides, which are topical compounds with a broad spectrum of activity against bacteria, viruses and fungi. Bacteria or viruses will be less likely to develop resistance to aganocides, a critical characteristic for antibiotics in today's environment. Because of its broad spectrum of activity, a highlight of NVC-422 is that the formulation may prove to be useful in treating bacterial conjunctivitis as well. Aganocides demonstrated high efficacy *in vitro* against multi-drug resistant bacteria, including MRSA and vancomycin-resistant *Enterococcus*.[13] NovaBay expects to complete its 450-patient, phase IIb trial in the first half of 2013.[14]

In addition, the Portuguese pharmaceutical company Adapt Produtos Oftalmológicos Ltda. is evaluating the efficacy and tolerability of ganciclovir ophthalmic gel 0.3% for the treatment of adenoviral conjunctivitis compared to placebo in an ongoing Phase III trial.[15]

Antiseptic Options

Antiseptics are used for surgical sterilization, treatment of infection, prophylaxis, and medication preservation. Endophthalmitis arising from cataract surgery is a rare but serious complication thought to derive largely from microflora in the ocular tear film, lids, and adnexa gaining entry to the anterior chamber during surgery.[16] Antiseptic biocides, such as povidone-iodine, may be an effective approach to anti-infective therapy. Antiseptics contain certain advantages because of their physicochemical mechanism of action, which includes their ability to act across broad swaths of pathogens, including strains of conjunctivitis caused by adenovirus.[17] Povidone-iodine is a broad-spectrum antiseptic that works by iodination of lipids and oxidation of cytoplasmic and membrane components; this chemically-based antimicrobial activity has little risk of microbial resistance, cross-over capabilities, and wide applications with high degrees of efficacy.

FST-100 (povidone-iodine/dexamethasone ophthalmic suspension, Foresight Biotherapeutics) is a combination drug that focuses on microbial eradication and reducing infection-related inflammation. As compared to cidofovir and tobramycin/dexamethasone, FST-100 showed superior clinical effectiveness and virucidal activity in a rabbit model.[18] Two randomized, double masked, multi-center studies are currently underway to test the safety and efficacy of FST-100 for the treatment of acute viral conjunctivitis.

Treatments and Future Therapies

Based on the pathogens involved, therapeutic agents may have a different impact on each infection. Even broad-spectrum antibacterials cannot eliminate all potential ocular pathogens. It would, therefore, be wise for clinicians to understand the difference between gram-positive and gram-negative bacteria and which antibacterial therapies are more effective against each type. The outermost cell component of gram-positive bacteria is a thick, rigid layer of peptidoglycan, and the exterior of gram-negative bacteria includes an additional liposaccharide layer.

To preserve efficacy, clinicians must employ antibiotic therapy carefully. Some strategies to slow the progress of resistance include cycling drugs, selectively using anti-infectives and combining different antibiotics. In one review, three out of four studies demonstrated that cycling reduced the rate of resistance to the class not in use.[19]

These new advances in ocular antimicrobial drugs show a leap toward innovation that we have not previously seen within this realm of therapy. Rather than bringing out the "new and improved" beta-lactam or macrolide, drug developers have emphasized an ever-diversifying array of antibacterial mechanisms of action. Fighting the good fight against bacterial resistance is not a battle that is easily won, but we are pushing towards the finish line for a Herculean, non-resistant drug. RCCL

Dr. Abelson, a clinical professor of ophthalmology at Harvard Medical School, consults in ophthalmic pharmaceuticals. Mr. Shapiro is vice president of anti-infectives and anti-inflammatories at Ora, Inc. Ms. Tobey is a medical writer at Ora, Inc.

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Additional references at www.reviewofcontactlenses.com.

What Else Can Contacts Do?

New developments in contact lens technology help eye care practitioners better fit current patients, reduce dropouts and simultaneously reach a new audience.

By Fiona Stapleton, Ph.D., MCOptom, and Nicole Carnt, Ph.D., BOptom

Technological advances have the potential to increase our worldwide contact lens wearer base—estimated currently to be roughly 125 million to 140 million lens wearers, and make headway into non-traditional markets and populations.[1] This broadening of the wearer base presents great opportunities, but also raises new clinical questions that will help identify future research agendas. In this article, we will discuss three areas of contact lens research: myopia control, safety and drug delivery.

Myopia Control

High myopia is a significant public health issue, particularly in Asian populations, and is associated with greater risk of retinal detachment, choroidal degeneration, glaucoma and early cataract.[2] There is some evidence that contact lens-related adverse events occur more often in high myopes, most likely due to increased reliance on contact lenses.[3,4]

Corneal reshaping techniques (CRT) were introduced in the early 1960s.[5] In the 1990s, new designs—e.g., reverse geometry and the use of high Dk materials—ensured sustained reproducible effects after overnight wear. Recent clinical trials have confirmed anecdotal reports of myopia retardation due to decreased axial length with CRT.[5,6]

There was early hope that alignment fitting rigid lenses would decrease myopia; however, randomized controlled trials indicated that there was only flattening of the cornea and no significant changes in axial length.[7] Adaption is less of an issue with overnight vs. daily wear of rigid gas-permeables. However, in addition to easy adaption, soft lens designs require less skill and specialized equipment to fit—thus broadening the market to reach a greater number of wearers.

A 2004 study found an association between low Dk soft lenses (but not high Dk silicone hydrogels) and an increase in myopia over time.[8] Soft bifocal lenses have shown good efficacy in myopes with high accommodative lag and esotropia.[9] Twin studies also indicate a beneficial effect in these groups.[10]

Recently, dual focus lenses that induced myopic defocus simultaneously with distance vision have shown

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promising results.[11] These lenses are marketed in Asia as MiSight daily disposable lenses (omafilcon A, CooperVision). Although the mechanism is unknown, it is thought to be related to reduced peripheral defocus rather than driven by reducing accommodative stimuli.

Hyperopic peripheral defocus as a stimulant to myopic progression has been established through animal studies.[12] Novel contact lenses correcting for peripheral hyperopic defocus are in clinical trials and have been shown to decrease myopic progression compared to spectacles.[12] While the decreases are modest, the results are promising. Increased research into eye shape and development is likely to fuel lens design innovations and improve outcomes.

There has been concern regarding the safety of overnight wear of corneal reshaping lenses following reports of microbial keratitis in East Asia in the early 2000s. It is understood that these cases occurred with overnight wear of low Dk lenses, which may not have been fitted or cared for appropriately.[13] Recent clinical trials and anecdotal reports indicate low levels of adverse events, albeit at early age.[14] With the current results, residual ametropia is likely to be an issue for the majority of children targeted. Long-term effects of reshaping the eye and extended years of lens wear in terms of ocular surface biocompatibility, encompassing the lids and conjunctiva as well as the cornea, should be monitored.

Recent investigations into one-year wear of corneal reshaping lenses in young adults (ages 18 to 30) showed corneal changes that were not reversible one month after ceasing wear, including increased endothelial polymegethism, thinning of Bowman's layer and sub-basal nerve plexus.[15]

As we learn more about the factors that contribute to myopia (i.e., light levels, nutrition, near work and genetics), it is probable that enhanced myopia onset and retardation results using contact lenses could significantly lower the proportion of severe myopes. We do still have lingering questions as to what age and level of refractive error is optimal to introduce contact lens wear. Well-designed, long-term controlled epidemiological studies, as well as continued animal and in vitro investigations, will be required to improve success and ensure that the long-term health of the anterior eye is not compromised to the extent that it is predisposed to adverse events or restricted in lens wearing options down the road.

Compliance and Safety

Microbial keratitis (MK) presents with less severity (0.5x) but the same incidence in daily disposables vs. other soft lenses.[16,17] The lower severity of MK in daily disposables suggests that the frequency of replacement may affect organisms differently. Specifically, eliminating the storage case may remove the source of environmental pathogens. This is important because environmental organisms are associated with a greater frequency of vision loss and more severe disease phenotype.[18] Keep in mind that the rate of MK varies with different daily disposable lens types, with etafilcon A having the lowest in a recent study.[17] This may be related to difficulties with lens removal with other lens types.[17]

Researchers concluded that the incidence of corneal erosions with lenses contaminated with gram-negative bacteria was comparable to the rate of microbial keratitis rates for different lens modalities.[18] In a clinical trial of 278 daily disposable wearers (etafilcon A, 1 Day Acuvue, Vistakon) over a 12-month period in India, no cases of corneal erosions occurred.[18] Mark Willcox, Ph.D., and colleagues found that gram-negative contamination of these daily disposable lenses also was the lowest compared to frequent replacement daily and extended wear lenses.[18]

Case reports of severe *Pseudomonas aeruginosa, Acanthamoeba* and fungal keratitis with daily disposables do exist in the literature.[19-22] As the market penetration increases and new lens types are introduced, we must continue to monitor infection and severe inflammation rates, and continue surveillance for emerging organisms.

A large-scale study of compliance in Canada and the United States found that daily disposable wearers were more compliant with the practitioner's recommended replacement schedule than their two-week and monthly counterparts.[23] The majority of non-compliant daily disposable wearers stated cost was the primary reason.[23] In the U.S., one-fifth of non-compliant wearers said they did not see any harm in not replacing lenses daily.[23]

These users may be tempted to wear the lenses overnight—doing so increases the chance of infection four-fold. Another common error is to place the lens back in the blister pack that contains no active disinfectant, which increases the chance of infection.[16] A record card review study in the U.S. found that a higher proportion of daily disposable wearers reported non-compliant overnight wear compared to other lens wear modalities.[24]

A recent study highlighted the dangers of reusing daily disposable lenses.[25] Twenty daily disposable wearers participants transferred their lenses back into the blister pack, and then into a new case with the blister pack solution, after a full day of wear on five occasions. In 95% of wearers, at least one lens was contaminated—the predominant

organism was the gram-positive staphylococci. Six out of the 20 wearers admitted to previous reuse of lenses from the blister packs. What we can learn is that continual daily disposable education is just as vital in this modality, particularly as users may believe they have less chance of complications and, therefore, take more risks.

Several contact lens manufacturers have recently introduced novel technologies, such as incorporating wetting agents within lenses and solution blister packs, and developing new lens materials and manufacturing techniques. These enhancements are designed to encourage new lens wearers to the market, reduce the dropout rate and improve the comfort of current wearers.

When disposable lenses were first introduced into the market, the rate of microbial keratitis was artificially high.[26] As more of the population were fitted with disposable lenses the rate fell. It is believed that the artificial increase in the infection rate can be attributed to a high number of lenses being fit as problem solvers and a higher proportion of new adopters who traditionally take more risks at that time; our studies have shown that indeed high risk takers are less compliant with lens care.[27] If the number of daily disposable wearers grows to encompass the majority of full-time contact lens users, we hope that the rate of microbial keratitis will fall once again.

Delivery Vehicles

The topical application of therapeutic agents to the anterior surface of the eye is fraught with problems, including compliance (particularly in chronic conditions such as glaucoma), high clearance through tears and poor penetration of the drug through the cornea—meaning that doses are high, and local toxicity as well as systemic absorption can result.[28] Slow, regulated delivery through contact lenses would improve efficacy by decreasing the reliance on drug compliance and increasing the contact time, which would lead to lower levels of therapeutic agents, less toxicity and a reduction in systemic side effects.

Furthermore, contact lenses are already used as bandages for persistent epithelial defects and other ocular surface reconstruction. Amniotic membranes that contain numerous nutrients, such as growth factors, are used in recalcitrant cases.[29] It seems logical then that nutrients and healing agents could be incorporated in the contact lens material to slowly leach out over time; this, in turn, could speed up the healing process.

Over the past four decades, we have seen the introduction of several new techniques: incorporating barriers (e.g., vitamin E), molecular imprinting, particle encapsulation such as using liposomes, forming inclusion complexes and dissolving drugs in high-pressure volatile liquids such as carbon dioxide.[28] Particle encapsulation is a commercially used technique to deliver comfort additives in contact lenses.

Let's concentrate on two promising technologies for therapeutic drug delivery: the incorporation of vitamin E as a barrier in contact lenses and molecular imprinting.

• ***Vitamin E barrier.*** Vitamin E, a hydrophobic liquid, is readily absorbed into soft lenses, including HEMA and silicone hydrogels, and forms aggregated bodies.[28] For hydrophilic drugs, such as timolol, vitamin E forms a diffusion barrier that slows down the release of the drug by forcing it to maneuver around the aggregates.

Conversely, hydrophobic drugs, such as dexamethasone, diffuse through the vitamin E bodies, which delays drug release. Silicone hydrogels have been more widely investigated because of their suitability for extended wear, a desired characteristic for maintained release of drug.

Drug diffusion in vitro studies show that, with around 35% vitamin E loading, timolol release is extended for 28 hours and dexamethasone for 150 hours (40x and 15x that of a standard lens, respectively).[30]

Similar results have been found with fluconazole (hydrophilic antifungal), while longer release profiles occur with cyclosporine (hydrophobic immune suppressant) because it has a large molecular weight and high affinity for vitamin E.[31] Less of a barrier is created with topical anesthetics because they adsorb and diffuse on the surface of vitamin E aggregates, and sustained release is only available for one day.

Timolol-loaded vitamin E lenses have been shown to lower IOP with minimal ocular surface disruption in a spontaneous glaucoma dog model; human clinical trials have not been conducted.[32] Although the drug release profiles are promising, human in vivo release and drug toxicity need to be assessed. Furthermore, in vitro tests show a reduction in oxygen diffusion and, to a greater extent, lowering of ion permeability—a minimum amount of which is required for lens movement on the eye.[33] With cyclosporine, changes in the lens's refractive index occurred during drug elution.[31] Modeling of these changes indicates that sufficient oxygen, lens movement and vision stability will be available to have negligent clinical impact, but clinical trials are required.

• ***Molecular imprinting.*** During polymer synthesis, a macromolecular structure or memory for a drug template is created to form the molecular imprint. Drug release is governed by the size of spaces between the

polymer chains, the drug molecule and drug/polymer interactions. Recent studies have indicated that the structure of the imprint, rather than drug itself, is predominantly responsible for the release profile; this indicates that the technique could be applied to a wide variety of small molecular weight drugs.[28] Furthermore, a therapeutic dose can be reloaded into the template, and lenses could then be worn both for daily use and extended wear.

An in vitro study using ketotifen fumarate—an antihistamine and mast cell stabilizer used for allergic eye disease—showed up to five-day release profiles with the conventional infinite sink method of diffusion measurement.[34] When the authors modeled a finite turnover condition similar to tear drainage and replenishment, they found that only 5% of the drug was released in five days compared to the infinite sink method.[34] This indicates that drug release may be sustained for longer than estimated from the conventional method, but this large variation needs to be confirmed in vivo.

Many low molecular weight hydrophilic drugs have been incorporated in molecular imprints, including timolol, norfloxacin and diclofenac sodium.[35] Recently, diclofenac sodium has been incorporated in a live or dynamic polymerase system that increases binding and delays release further.[36]

High molecular weight molecules pose more of a challenge, but the comfort molecule hyaluronic acid (HA) has been incorporated in nelfilcon A and is available commercially as Focus Dailies with Aqua Comfort Plus (Alcon).[37] This technique used a biomimetic approach, using replications of an HA binding site in the molecular imprint to create higher affinity of HA with the lens.

Other in vivo work using molecular imprinted-contact lenses is limited; there is only one reported rabbit study using timolol-loaded lenses.[38] In vitro challenges such as changes to optical clarity, oxygen transport and mechanical properties in some networks have been reported.[38] Clearly, for promising molecular imprinted lenses, the next step should be in vivo testing of single and combination agents.

Contact lenses are primarily medical devices to correct refractive error while in situ. The extension of contact lenses as a device to prevent or slow down myopia and for use as a drug delivery vehicle broadens the population that may benefit from contact lens use. While comfort and vision are important considerations, the contact lens industry and eye care practitioners have a primary obligation to ensure lens safety is optimum, particularly for these possibly more vulnerable populations. RCCL

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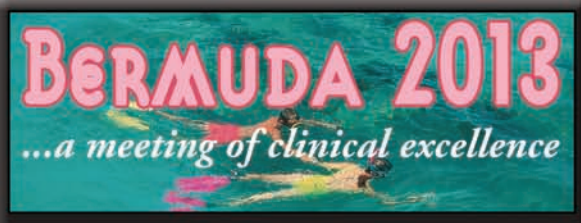

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