NOVEMBER/DECEMBER 2019

RCCL®

REVIEW OF CORNEA & CONTACT LENSES

CORNEAL DISEASE ISSUE

Unlocking the Mystery of CORNEAL DYSTROPHIES

Optometrists are often the first to detect the clues and sleuth out the diagnosis. Here's what to look for.

EARN 1 CE CREDIT

Page 28

ALSO:

It’s amazing how something so small
can make such a big impact.


SMALL?
PERHAPS.
SIGNIFICANT?
ABSOLUTELY.
HIGH OXYGEN TRANSMITTANCE
EXCEPTIONAL COMFORT
EXCELLENT VISION
RESERVED FOR VSP NETWORK DOCTORS
UNITY BIOSYNC WITH HYDRAMIST RATED...*
9 OUT OF 10
FOR OVERALL VISION
9 OUT OF 10
FOR INITIAL COMFORT
8 OUT OF 10
FOR OVERALL COMFORT
unity® WITH HYDRAMIST™ biosync™
ONE-DAY SILICONE HYDROGEL SPHERICAL CONTACT LENSES
Visit unitybiosync.com for more information or to order your fit kit today.
©2019 Vision Service Plan. Unity is a registered trademark of Plexus Optix, Inc. BioSync and HydraMist are trademarks of Plexus Optix, Inc.

contents

Review of Cornea & Contact Lenses | November/December 2019

departments

features

BAUSCH + LOMB
See better. Live better.

Zenlens™

#1 DOCTOR-PRESCRIBED SCLERAL LENS*

BALANCE *POWER AND SIMPLICITY*

SIMPLIFIED FITTING
with SmartCurve™ technology

FCLSA-CERTIFIED CONSULTANTS
offer individualized support

EXPANDED OFFERINGS
with Tangible® Hydra-PEG® and Zen™ Multifocal

*Based on US lens sales between December 2018 and February 2019.

IN BRIEF

■ Researchers recently found that **a conjunctival limbal autograft can provide long-term ocular surface stability and good visual outcomes for patients with unilateral total limbal stem cell deficiency**. After performing penetrating or deep lamellar anterior keratoplasty in 44.5% of eyes, best-corrected visual acuity improved from about 20/400 preoperatively to about 20/70 at last follow-up. The study noted two significant side effects: microbial keratitis in 14.8% of eyes and ocular hypertension secondary to corticosteroid use in 25.9%.

Eslani M, Cheung AY, Kurji K, et al. Long-term outcomes of conjunctival limbal autograft in patients with unilateral total limbal stem cell deficiency. Ocul Surf. September 6, 2019. [Epub ahead of print].

■ An Australian study determined that corneal and intra-epidermal neuronal loss was more pronounced in advanced diabetic retinopathy (DR) stages, indicating a **positive severity correlation between DR and diabetic peripheral neuropathy**. The corneal nerves, however, were far more sensitive to DR changes than the neuroretinal layers were. Corneal nerve fiber length and density were significantly reduced more so in the proliferative DR group than in the non-proliferative DR group. The researchers also found a low correlation between intra-epidermal and corneal fiber loss for both neurological scores.

Hafner J, Zadrazil M, Grisold A, et al. Retinal and corneal neurodegeneration and its association to systemic signs of peripheral neuropathy in type 2 diabetes. Am J Opthalmol. September 19, 2019. [Epub ahead of print].

■ Researchers recently found a **potential relationship between psoriasis and keratoconus**: the more severe the psoriasis, the greater the topography map changes, with the association persisting both in the beginning stages of the disease and the longer it lasts. They discovered that 26 eyes of 16 patients with psoriasis were keratoconus (KC) suspects, and another two eyes already had a diagnosis of KC. Although the results do not necessarily mean that patients with psoriasis will definitely experience KC at some point in their lives, the researchers suggest that **it would be useful to conduct eye examinations more often for these patients**.

Akcam HT, Karagun E, Iritas I, et al. Keratoconus could be associated with psoriasis: novel findings from a comparative study. Cornea. September 30, 2019. [Epub ahead of print].

Dry Eye: Look Beyond the Lenses

The root of many contact lens wearing patients' dry eye symptoms may not be the lenses but a different etiology entirely. While contact lens wear is an established cause of dry eye, a recent study found nearly half of symptomatic contact lens wearers had symptoms of dry eye that were not contact lens–induced.

The investigation enrolled 92 participants who completed the Berkeley Dry Eye Flow Chart with and without their lenses. Other testing included ocular surface exams and dry eye questionnaires.

The study divided the subjects into three groups: asymptomatic contact lens wearers; symptomatic contact lens wearers who became asymptomatic after they removed their lenses; and symptomatic lens wearers who did not improve after they stopped wearing their contacts.

The investigators found 40% of subjects were asymptomatic, 33% had contact lens–induced dry eye and 27% had underlying physiological dry eye.The researchers noted the Visual Analog Scale ratings, Ocular Surface Disease Index and Standard Dry Eye Patient Questionnaire scores were significantly better for the asymptomatic group but did not distinguish contact lens–induced dry eye from physiological dry eye.

Additionally, the study found the physiological dry eye group was significantly worse than both the lens-induced dry eye and asymptomatic groups in pre-corneal noninvasive tear break-up time (8.2 seconds in the physiological group vs. 12.3 seconds in the contact-lens induced group and 14.3 seconds in the asymptomatic group), anterior displacement of the line of Marx and superior conjunctival staining.

The asymptomatic and lens-induced dry eye groups showed similar clinical signs, whereas the contact lens–induced dry eye and physiological dry eye groups were more similar in reported symptoms.

Many contact lens wearers presenting with dryness symptoms have an underlying dry eye condition and won't respond to treatments aimed at changing lenses or solutions, the researchers said. Contradictory results from research studies of dry eye in contact lens wearers could be due in part to a failure to distinguish subjects with symptoms resulting from contact lens wear from those whose symptoms have underlying causes unrelated to contact lens wear.

"It is critical for clinicians and researchers both, once a contact lens wearer has presented with symptoms, to investigate further using a combination of questionnaire instruments, clinical assessments and objective measurements to determine the underlying causes or contributing factors to achieve successful patient treatment and valid, generalizable clinical study results," the researchers wrote in their paper on the study.

Photo: Heidi Wagner, OD, MPH

Changing lenses or solutions might not affect dry eye in CL wearers.

Molina K, Graham AD, Yeh T. et al. Not all dry eye in contact lens wear is contact lens-induced. Eye Contact Lens. September 10, 2019. [Epub ahead of print].

Location Plays Key Role in Understanding Corneal Pain

Neuropathic pain felt on the periphery or in the center of the cornea may be two distinct issues that respond differently to topical anesthesia, specifically if the pain presents without clinically visible cues, a study reports.

The investigation included 27 eyes of 14 patients who had continuous severe ocular pain but with minimal or no ocular surface signs for at least one year. The patients were also non-responsive to topical lubricants, steroids or cyclosporine.

The investigators used *in vivo* confocal microscopy to examine the central and paracentral cornea in the patients with corneal pain and in seven healthy controls. The researchers also measured corneal epithelial thickness and sub-basal nerve density.

The study found four patients responded to topical anesthesia (the responsive group), indicating peripheral neuropathic corneal pain, while 10 patients showed no improvement (non-responsive group), which pointed to central neuropathic corneal pain.

The investigators also reported the Schirmer 1 was within normal limits in the responsive group but was significantly greater in the non-responsive group. None of the other clinical parameters or corneal epithelial thickness were markedly different.

They also noted that the sub-basal nerve density was significantly reduced in corneal pain patients compared with controls, and the stroma of all study participants showed activated keratocytes and spindle, lateral and stump microneuromas. The study observed a much greater amount of microneuromas and activated keratocytes in the responsive group compared with the non-responsive group.

Neuropathic corneal pain without visible clinical signs does not represent typical dry eye disease, the researchers added.

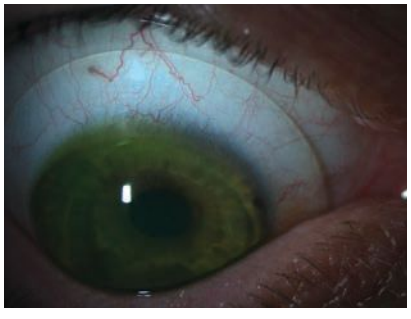
Ross AR, Al-Aqaba MA, Almaazmi A, et al. Clinical and *in vivo* confocal microscopic features of neuropathic corneal pain. Br J Ophthalmol. September 18, 2019. [Epub ahead of print].

Scleral Lens Terminology Guide Developed

Confused by scleral lens jargon? If so, you're not alone. With no current scleral lens standards, a handful of optometrists sought to provide lens fitting and manufacturing definitions to improve uniformity between manufacturers and lens handlers.

A committee of 12 advanced scleral lens clinicians used a literature review to help them develop a list of terms related to scleral lens fitting and manufacturing. After experts in the field were consulted to validate the terms and their suggested definitions, a final version was adopted by the Scleral Lens Education Society at the end of last year.

The original team behind this undertaking, led by Langis Michaud, OD, MSc, provided the definition of a scleral lens, addressed the general terminology habitually applied to scleral lenses and described terms specifically used when fitting and manufacturing scleral lenses. They then made recommendations to manufacturers about the essential elements eye care practitioners need to help them understand the lens design and customize their fit.



Standardized scleral lens fitting and manufacturing terms aim to improve clarity in the field.

"A common language is key to advancing the science and clinical practice of scleral lens fitting," they concluded in their paper on the effort. "The current terminology will help standardize this field, helping eye care practitioners, educators, speakers and manufacturers to talk with the same language."

"I am very proud of this article because it sets the standard for the scleral lens industry," Dr. Michaud says. "From now, hopefully, every stakeholder will speak the same language for a better understanding. It also highlights the evolution of the field in the past years. Now, as an evolved market, scleral lenses should rely on an official terminology." RCCL

Michaud L, Lipson M, Kramer E, et al. The official guide to scleral lens terminology. Cont Lens Anterior Eye. September 25, 2019. [Epub ahead of print].

CL Patients Can Adapt Faster

For new contact lens wearers, eye care practitioners typically recommend a gradual wearing schedule to help patients adapt to lens wear. But a team of UK researchers suggests this conventional strategy may no longer be needed with some of the latest soft contact lens designs.

Their study, published in *Contact Lens & Anterior Eye*, found no difference in fast vs. gradual adaptation in patients who wore daily disposable hydrogel or silicon hydrogel (SiHy) contact lenses.

The investigation randomly assigned patients to an adaptation schedule, either fast (10 hours of wear the first day) or gradual (four hours on the first day and two extra hours each day until reaching 10 hours). In the hydrogel lens group, 24 patients were put on the fast schedule, and 21 wore their lenses on a gradual schedule. The SiHy group included 10 patients on the fast schedule and 10 who were on the gradual schedule.

Masked investigators graded ocular surface physiology and non-invasive tear break-up time. They also recorded a range of subjective scores at the initial visit, after 10 hours of lens wear, four to six days later and 12 to 14 days later.

The study found no difference in ocular surface physiology between the fast and gradual adaptation groups at any time point in either lens type. The researchers also found non-invasive tear break-up time was similar at all time points for both adaptation groups in both lens types with the exception of gradual adaptation SiHy wearers, whose times were slightly longer than the fast adaptation group at 12 to 14 days.

The study noted the subjective scores were similar across the visits and lens types with the exception of "lens awareness" and "ease of lens removal," which were better in the fast group compared with the gradual adaptation group of hydrogel lens wearers at day seven. Additionally, the fast hydrogel lens group reported less end-of-day discomfort 12 to 14 days compared with the gradual adaptation group.

"There appears to be no benefit in daily disposable soft contact lens adaptation for neophytes with modern contact lens material," the researchers wrote in their paper. They also noted that no underpinning scientific evidence existed for the need for a gradual approach for new lens wearers.

Wolffsohn JS, Dhirajlal H, Vianya-Estopa M, et al. Fast versus gradual adaptation of soft daily disposable contact lenses in neophyte wearers. Cont Lens Anterior Eye. September 20, 2019. [Epub ahead of print].

CORNEAL NERVES SAFE

Upon evaluating corneal sub-basal nerve alterations in contact lens-naive silicone hydrogel lens wearers and investigating the relationship between structural changes and corneal sensitivity, researchers found that sensory adaptation to lens wear is not mediated through attenuation of the subbasal nerve or reduction of corneal tactile sensitivity.

Kocabeyoglu S, Colak D, Mocan M, et al. Sensory adaptation to silicone hydrogel contact lens wear is not associated with alterations in the corneal subbasal nerve plexus. Cornea. 2019;38(9):1142-6.

RCCL® REVIEW OF CORNEA & CONTACT LENSES

11 Campus Blvd., Suite 100
Newtown Square, PA 19073
Telephone (610) 492-1000
Fax (610) 492-1049

Editorial inquiries: (610) 492-1006
Advertising inquiries: (610) 492-1011
Email: rccl@jobson.com

EDITORIAL STAFF

EDITOR-IN-CHIEF
Jack Persico jpersico@jobson.com
MANAGING EDITOR
Rebecca Hepp rhepp@jobson.com
ASSOCIATE EDITOR
Catherine Manthorp cmanthorp@jobson.com
ASSOCIATE EDITOR
Mark De Leon mdeleon@jobson.com
CLINICAL EDITOR
Joseph P. Shovlin, OD, jpshovlin@gmail.com
ASSOCIATE CLINICAL EDITOR
Christine W. Sindt, OD, christine-sindt@uiowa.edu
EXECUTIVE EDITOR
Arthur B. Epstein, OD, artepstein@artepstein.com
CONSULTING EDITOR
Milton M. Hom, OD, eyemage@mminternet.com
GRAPHIC DESIGNER
Ashley Schmouder aschmouder@jobson.com
AD PRODUCTION MANAGER
Scott Tobin stobin@jhihealth.com

BUSINESS STAFF

PUBLISHER
James Henne jhenne@jobson.com
REGIONAL SALES MANAGER
Michele Barrett mbarrett@jobson.com
REGIONAL SALES MANAGER
Michael Hoster mhoster@jobson.com
VICE PRESIDENT, OPERATIONS
Casey Foster cfoster@jobson.com

EXECUTIVE STAFF

CEO, INFORMATION SERVICES GROUP
Marc Ferrara mferrara@jhihealth.com
SENIOR VICE PRESIDENT, OPERATIONS
Jeff Levitz jlevitz@jhihealth.com
SENIOR VICE PRESIDENT, HUMAN RESOURCES
Tammy Garcia tgarcia@jhihealth.com
VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
Monica Tettamanzi mtettamanzi@jhihealth.com
VICE PRESIDENT, CIRCULATION
Emelda Barea ebarea@jhihealth.com
CORPORATE PRODUCTION MANAGER
John Caggiano jcaggiano@jhihealth.com

By Joseph P. Shovlin, OD

New Contacts, Same Old Mistakes

Besides learning from the consequences, how can patients better understand compliance?

A sobering report this past summer by Centers for Disease Control and Prevention (CDC)'s *Morbidity and Mortality Weekly* Report highlighted that "one-third of lens wearers recalled never hearing any lens care recommendations–even though most eye care providers reported sharing recommendations always or most of the time with their patients."[1] There is hope that we will continue to provide ongoing proper lens care education in order to ward off potential risks of complications, especially serious eye infections, but how will the estimated 45 million contact lens wearers in the United States listen?

As eye care professionals, we are acutely aware that improper wearing schedules and poor care behaviors may pose devastating risks to patients wearing contact lenses. Adding another dimension, engaging in hazardous behaviors does not appear to be totally related to a general lack of knowledge.[2] Risky behaviors in lens wearers unfortunately abound, even when seemingly appropriate and adequate knowledge of lens care exists. The most common reasons for non-compliance in lens wearers are saving money and forgetting the recommended lens replacement schedule.[2] How quickly patients seem to forget or shrug off our warnings.

Nevertheless, non-compliant behavior continues to pose risks to our patients and hinders efforts to maximize safety.[3] Historical rates of non-compliance in lens wearers range from 40% to 91%, but one model found that only 2% of patients surveyed demonstrated "good" compliance and only 0.4% were "fully" compliant.[3]

Fortunately, these behaviors are modifiable with continued efforts from all of us. So, continue to stress the risks of:

1. improper wearing schedules
2. not complying with recommended lens replacement frequencies
3. not washing and drying hands before inserting and removing lenses
4. re-using or "topping-off" lens care solutions
5. not cleaning properly and replacing lens storage case properly or regularly
6. not rubbing or rinsing lenses with approved lens care solutions
7. swimming and showering in contact lenses and exposing them to contaminated water
8. sleeping in lenses when not approved to do so

The CDC and others have done a fabulous job in providing educational resources and other communication materials about healthy lens care habits that can be displayed in the office and handed or shown to patients. Employing both verbal and written messages seems to be a more effective in communicating with patients and consumers.[2]

In addition, the CDC has designated a week in August (prior to students returning to school) the past few years as Contact Lens Health Week to emphasize the importance of healthy behaviors in lens care. The CDC recommends combating poor compliance by using techniques that are easy to understand and specific to the message intended, such as repeating messages that minimize jargon and checking for patient understanding of the presented points.[1]

Practice newsletters, text messages and email missives to your patients may serve as reminders on how to avoid risky behaviors, as well as why compliance is important and the risks of not complying. Unfortunately, the strongest message is heard when a patient experiences a complication, which then provides an opportunity to get that patient's attention by reviewing what might have contributed to their lens-related complication.

We must continue compliance campaigns with ongoing pertinent messages that sustain and encourage healthy behaviors. Only then can we potentially avoid the tragic complications that often result in sight-threatening experiences for our patients. Future studies will judge just how effective compliance campaigns really are. Can they be totally effective? Probably not, for a whole host of reasons—but the fight must go on. It's just too important not to make this a major crusade! RCCL

1. Konne NM, Collier SA, Spangler J, Cope JR: Healthy contact lens behaviors communicated by eye care providers and recalled by patients-United States, 2018. MMWR Morb Mortal Wkly Rep. 2019;68(32):693-7.

2. Steele K. Contact lens compliance: a review. Contact Lens Update. contactlensupdate.com/2018/10/26/contact-lens-compliance-a-review. October 26, 2018. Accessed October 3, 2019.

3. Robertson DM and Cavanaugh D: Non-compliance with contact lens wear and care practices: a comparative analysis. Optom Vis Sci. 2011; 88(12):1402-8.

By Robert Ensley, OD, and Heidi Miller, OD

GPs: Now and Beyond

A conversation with prolific GP expert Ed Bennett, OD, on what these lenses still have to offer.

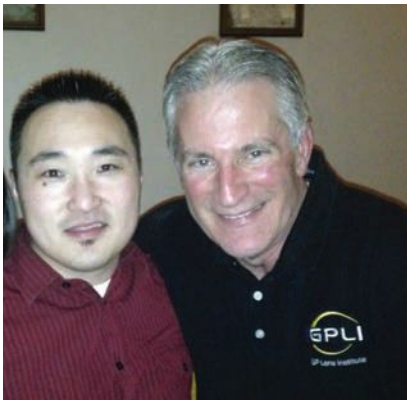
This year marked the retirement from academia of one of the true legends of GP lenses, Ed Bennett, OD. For nearly 40 years, Dr. Bennett has served as a clinician, researcher, educator, industry leader and mentor to many. Recently, we picked his brain about how the GP lens industry has evolved over his career and what he expects for its future.

First off, congratulations on your retirement from the University of Missouri-St. Louis after 37 years! Where did you develop your passion for GP lenses? Was there a particular professor or patient that inspired you?

I've been a rigid lens wearer for more than 52 years, and I personally knew the benefits. When I was fortunate enough to be a fourth-year extern in a newly developed contact lens research externship at Indiana University under the supervision of Drs. Sarita Soni and Irvin Borish. That was life-changing.

I was involved in FDA clinical trials for the first extended-wear lenses, the first soft toric and, most importantly, the first viable gas permeable lens, Polycon I (Art Optical Lens). I was able to observe the edema dissipate in hundreds of polymethylmethacrylate-wearing patients who were refit into GP lenses during my three years on the faculty at Indiana University. And I was hooked!

At one point, many opined that GP lenses would also become obsolete. What factors do you believe have led to their longevity and survival?



Dr. Bennett with Dr. Ensley.

I certainly remember the 'obsolete' comments, and I am so excited that idea never came close to fruition. Certainly, the revival—and continuing improvement—of scleral lenses has had a significant impact and will continue to do so well into the future.

I've seen GP materials advance such that we have stable and wettable lenses, even in as high as 200 Dk. The introduction of the HydraPEG (Tangible Science) coating allows for these lenses to be worn comfortably for longer time periods and aids with the borderline dry eye patients.

In your opinion, what were the greatest innovations in GP lens technologies that have impacted the industry?

Regarding the aforementioned scleral lenses, there are innovations such as molded sclerals and topography-aided, stable, hyper-Dk lens materials and lens coatings. There is continuing improvement in orthokeratology (ortho-K) designs and GP multifocal designs, especially hybrids and sclerals. Major improvements in manufacturing technology resulting in ultrathin and pseudo-aspheric peripheral designs have all been important as well.

Are there any challenges we still face in GPs that you feel can be improved upon?

Of course, the elephant in the room has always been a patient's initial comfort. Early on, I was involved in a number of studies looking at the relationship between lens design factors and comfort, and the only factor that was significant was diameter. Scleral lenses ultimately supported that finding.

However, we did also find in another study that the use of a topical anesthetic was significant in optimizing a patient's initial experience along with how you presented GPs to a patient. If the optometrist's presentation to the patient was proactive and used terms such as "lens awareness" and "lid sensation" as opposed to "discomfort," they were more likely to be successful.

Today's lower edge clearance and consistently smooth edge profile designs have resulted in well-centered, better initial comfort results than their predecessors. This is especially important with patients benefiting from the vision achieved with GP bitoric, multifocal and keratoconus/post-surgical designs, and I hope this will continue.

Do you think the online marketplace will ever become a competitor with GP lenses?

It's difficult to say at this time, but my inclination is no. Obviously the

online marketplace will continue to grow, but one of the strengths of GP lenses is their custom nature, which simply does not lend itself easily to the online marketplace.

GP lenses are often perceived as more time consuming and difficult to fit. What advice would you give to a practitioner wanting to build their GP practice?

For the practitioner desiring to start building their GP practice, I would first encourage them to talk to one or more of the Contact Lens Manufacturer's Association (CLMA) member laboratories about the services and lenses they can provide. Their consultants truly are supportive, and there is no question too simple for them to answer. With the ability to take pictures and videos of lenses on the eye via iPhone slit lamp adapters, as well as corneal topography, providing the laboratory with this information can lead to great success.

The GP Lens Institute (GPLI, www.gpli.info) has a large number of online resources in all areas (spherical, multifocal, toric, irregular cornea, scleral and ortho-K), including video tutorials, calculators and almost 100 archived webinars. There is also a lab consultants FAQs module as well as a coding and billing module.

You have also served in many positions and leadership roles. What are you planning on staying involved with in this next phase of life?

I'm still keeping busy. As executive director of the GPLI, my intent is to increase my time in helping develop new GP and custom soft lens resources and programs. I'm still in an editorial position for a contact lens publication, and I definitely enjoy that role. Likewise, I hope to continue to serve on the Education Committee of the Global Specialty Lens Symposium.

The fifth edition my text with Vinita Henry, *Clinical Manual of Contact Lenses*, is coming out any day now. I'm also excited to be joining a new oversight committee for the AAO in anticipation of their 100th anniversary in 2022. And who knows? There might be something else out there for me to be active in.

Care to offer up any projections for the future of GP lenses in the next 25 years and beyond?

Certainly, scleral lenses will continue to grow and—with the innovations in design including peripheral haptics as well as profilometry—they will become easier and result in higher patient success. We will see continued design innovations in presbyopia with corneal, scleral and hybrid multifocals, including decentered optics to optimize vision at all distances.

Dr. Bennett with Dr. Miller.

Myopia control is on the verge of exploding onto the scene, and it only makes sense that ortho-K will have a significant role, as its designs continue to improve. And GP lenses lend themselves to the augmented/virtual reality lenses now under development, as well as possibly being used as a recording device.

Can you single out any aspect of your career in GP lenses that has been the most rewarding? Did you ever think you would become so influential amongst GP lens industry?

Thirty-two years ago, Carl Moore, then-president of the CLMA, was taking me to the airport. He asked if I would be interested in becoming executive director of the GPLI.

Taking that position was the greatest professional decision I have ever made and has brought me an enormous amount of personal satisfaction. What a joy to be able to have a passion for something and live out that passion surrounded by those who feel the same way, most notably the CLMA board and representatives and our outstanding GPLI advisory board—many of the most knowledgeable GP experts in the world.

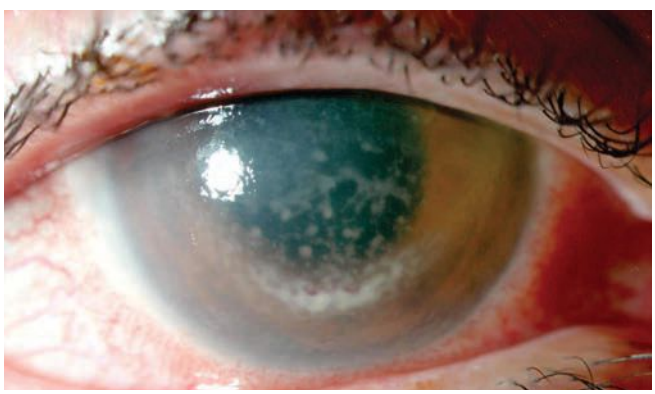
It's been a wonderful life to have been able to serve the profession in several leadership positions and to be able to author articles and textbooks, but it is the opportunity to work for the CLMA in my present capacity that has allowed me to have any influence I might possess—and to follow my dreams! RCCL

Herpetic Keratouveitis Front to Back

Don't forget to check the posterior segment to catch the worst manifestation.

A 56-year-old female was sent in for a cornea evaluation by her primary optometrist. He was concerned by the progression of an increasingly severe keratitis in her right eye. Treatment was initiated four weeks ago with topical trifluridine 1.0%. When the eye didn't respond, topical tobramycin 0.3% solution was added. Though the patient had significantly reduced vision, she was not in any pain. She had undergone cataract surgery uneventfully on both eyes three years earlier and only wore progressive lenses for reading purposes.

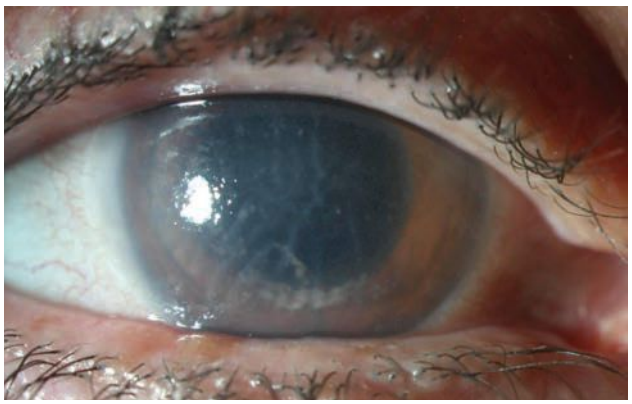
When corrected, the patient's vision was "hand motion at five feet" OD and 20/25 OS. There was no improvement with pinhole testing on the right eye. The patient had a full range of motion, but full evaluation of pupils and confrontation fields was not possible due to poor direct views of the right pupil and markedly reduced visual acuity (VA), though a consensual response of the left pupil when light was applied to the right was present. Her intraocular pressures were 20mm Hg OD and 8mm Hg OS.



Superficial peripheral keratitis.

PRELIMINARY TESTING

The patient's exam showed 1+ lid edema, 3+ injection of the conjunctiva, a superior superficial crescentic marginal infiltrate from 11 o'clock to 2 o'clock, 2+ diffuse epithelial edema and 4+ granulomatous keratic precipitates in a partial ring distribution. Her endotheliitis was intense enough to cause some red blood cells to precipitate as well.



Intense endotheliitis with placoid and partial ring precipitation of white and red blood cells on the corneal endothelium.

Views of the anterior chamber (AC) were limited, but 1+ to 2+ white cells were graded, the iris was normal without segmental atrophy and the patient's intraocular lens was in a good position. The full dilated exam showed a grossly normal but poor view of the optic nerve, retinal vessels, macula and retinal periphery due to poor corneal optics. The fellow eye was unremarkable with the exception of pseudophakia.

PROBLEM AND SOLUTIONS

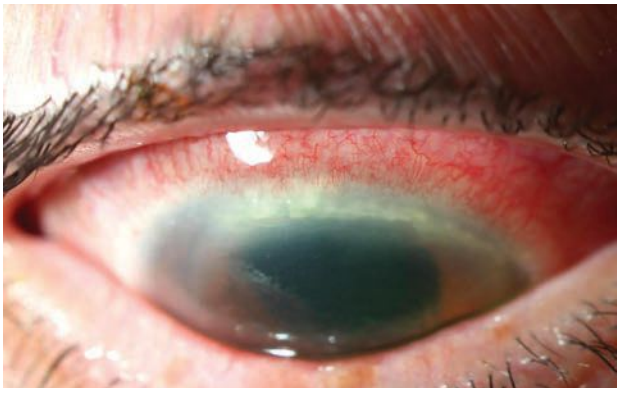
Marked unilateral keratouveitis/endotheliitis in an adult without any other risk factors is most likely herpetic in origin, so I questioned the patient about a history of herpetic eye disease, which she denied, and cold sores, which she had developed somewhat frequently in the past.

Though the peripheral keratitis was unusual for the diagnosis (and would be more typical of herpes zoster keratouveitis), my working diagnosis was severe diffuse herpes simplex virus (HSV) endotheliitis and uveitis, as the patient had no known history of zoster-based periocular infection. She was placed on homatropine 5% BID, Durezol (difluprednate, Novartis) hourly and oral acyclovir 400mg five times per day and scheduled to follow-up the next day. She was also instructed to discontinue topical anti-infective medication usage, as I felt that after being dosed for about a month, they might be causing superficial stress to the cornea and contributing little therapeutic value.

At subsequent follow-ups, we could see that the patient's corneal and AC pathology was slowly responding to therapy and vision was gradually improving. As corneal

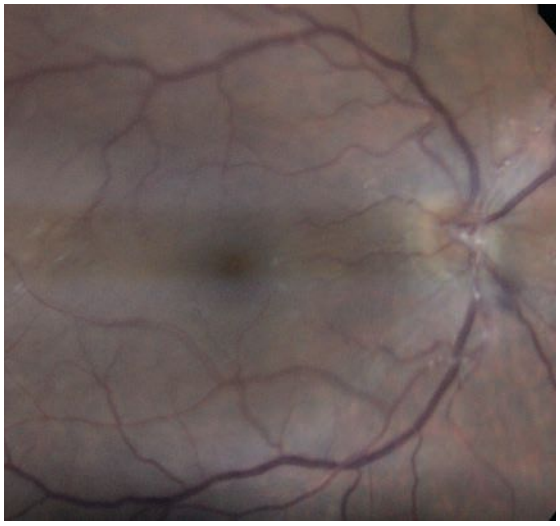
optics improved, so did posterior segment views. With these better views, it became apparent that the patient's posterior segment was also involved to some degree. There was mild vitritis, an asymmetrically mildly hyperemic nerve and a small amount of segmented columnar occlusive material in the primary and secondary retinal arterioles.

Given the previous diagnosis and now posterior involvement, acute retinal necrosis (ARN) needed to be considered. ARN is a rare pathology caused by herpes viruses that produces a diagnostic triad of edematous necrosis of the retina, occlusive vasculitis/arteritis and vitritis. It carries an extremely negative prognosis—it's estimated that between 20% and 85% of ARN patients develop rhegmatogenous retinal detachment and nearly 50% of patients end up with a best-corrected VA of 20/200 following the condition.[1] Due to the severity of the possible problem and its location in the posterior segment, the patient was maintained on topical therapy and referred to the University of Washington Uveitis Clinic.



Improvement in corneal involvement after one week of aggressive therapy.

At the clinic, posterior involvement of the patient's uveitis with diffuse retinal vessel leakage, subclinical retinal edema and nerve head leakage was confirmed. The specialist described the arteriolar involvement as Kyrieleis plaques, which are a source of retinal vasculitis associated with ARN, tuberculosis, syphilis toxoplasmosis and Mediterranean spotted fever. Serology tests for these pathologies were run and subsequently found to be negative.



Posterior segment involvement shows occlusive arteritis of the primary retinal arterioles. These Kyrieleis plaques are associated with ARN.

The primary diagnosis of HSV keratouveitis with possible early ARN was maintained. Given the absence of zonal retinal necrosis, a firm diagnosis of ARN was not made, so its treatment protocol, which involves prophylactic vitreoretinal surgery, was not followed. The uveitis facility added a modest dose of oral prednisone with a protracted taper and asked us to schedule follow-ups every six weeks.

OUTCOMES

After six months of follow-up and gradually tapering therapy, the patient's panuveitis fully resolved. She now corrects to 20/20 and is very pleased with the outcome.

This case is a good reminder of an important clinical pointer. While the scope of possible pathologies of herpetic eye disease is wide and the vast majority of cases only involve the anterior segment, the disease's worst manifestation involves the posterior segment. Therefore, periodic posterior evaluation of these eyes is necessary. Though it is easy to focus only on the anterior exam when working with impressive cases of anterior uveitis, the clinician needs to recognize that these pathologies should not be presumed to only involve the anterior segment. Paying equal close attention to the posterior segment is critical to catch panuveitis, which is associated with more profound and longer-lasting vision loss. RCCL

1. Schoenberger SD, Kim SJ, Thorne JE, et al. Diagnosis and treatment of acute retinal necrosis: a report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(3):382-92.

HOT TOPICS in Bacterial Keratitis

By Christina Cherny, BS, Pratik Patel, OD, and Suzanne Sherman, OD

Understanding **common pathogens** and **effective treatments** is essential in managing these patients with the most successful results.

Bacterial keratitis is a serious ocular condition that can lead to vision loss if not treated promptly, appropriately and aggressively.[1] According to the CDC, an estimated one million clinical visits occur annually in the United States due to keratitis.[2] Significant risk factors include contact lens use and ocular surface disease. Contact lens risk factors can be further broken down into overnight lens wear, poor storage hygiene and infrequent storage case replacement.[2,3]

Treatment of bacterial keratitis begins with empirical management using frequent instillation of topical broad-spectrum antibiotics for coverage of both gram-positive and gram-negative pathogens. Common treatment starting points depend on the severity of the corneal ulcer and consist of monotherapy with fluoroquinolones or combination therapy with cephalosporins, aminoglycosides, vancomycin, amikacin or fortified antibiotics.[1,4] This increased first-line usage of broad-spectrum antibiotics, however, has coincided with a significant rise in the number of bacterial pathogens resistant to antimicrobials.[5]

In this review, we discuss relevant trends in bacterial keratitis, including corneal pathogen prevalence, corneal pathogen susceptibility, antibiotic resistance and treatment strategy.

PREVALENCE

According to two long-term retrospective case reviews of microbial keratitis in the United States, gram-positive organisms were the most commonly isolated bacterial group, followed by gram-negative organisms.[6,7] Both studies indicated *Staphylococci* as the most prevalent gram-positive organism and *Pseudomonas* species as the most frequently isolated gram-negative and overall organism.[6,7] The individual proportions of cultured species differed slightly by study.[6,7] Another study noted that methicillin-resistant *Staphylococcus aureus* (MRSA) comprised 20% of all isolates, while 5% of all cultured isolates were MRSA.[6]

International studies show similarities and differences in bacterial prevalence compared with national findings.[8-15] Similar to the United States, investigations in China, Switzerland, South Korea, Spain and Colombia indicate an overall preponderance of gram-positive organisms, as well as a predominance of *Staphylococci* and *Pseudomonas* individual strains.[10,12,14,15] India,

ABOUT THE AUTHORS

Ms. Cherny is a third-year optometry candidate at the SUNY College of Optometry, where she is completing an Advanced Cornea and Contact Lens micro-credential. She received her undergraduate Human Biology, Health and Society degree at Cornell University. She is interested in specialty contact lenses and corneal disease management.

Dr. Patel is a graduate of the SUNY College of Optometry. He completed a contact lens and ocular disease residency at The Ohio State University Havener Eye Institute. He is currently a clinical instructor at Weill Cornell Medicine Ophthalmology in New York City, where his focus is anterior segment management and specialty contact lens fitting. He is a fellow of the American Academy of Optometry.

Dr. Sherman is an assistant professor of optometric sciences in ophthalmology, director of optometric services at the Columbia University Medical Center and an assistant attending at New York–Presbyterian Hospital. She specializes in complex and medically necessary contact lens fittings, anterior segment disease and primary care. She is board-certified by the American Board of Optometry and National Board of Examiners in Optometry. She is a fellow of the American Academy of Optometry, conducts research, contributes to peer-reviewed scientific publications and presents at annual meetings.

Taiwan and the tropics of Malaysia share another similarity with the United States—*Pseudomonas* was the single most commonly isolated bacterial organism.[8,11,13] Of notable contrast to the aforementioned countries is Taiwan. From 2007 to 2016, Taiwan noted gram-negative bacteria as the most commonly isolated strain, followed by gram-positive bacteria.[13]

Temporal trends in the prevalence of gram-positive strains isolated from bacterial keratitis cases varied by each respective region. In the United States, there was a 1.13-increased odds of culturing MRSA for each one-year increase in culture date.[6] The trends for gram-negative organisms also varied considerably by region and species. According to one study, the only bacterial pathogen that increased significantly in proportion during the study period was *Pseudomonas aeruginosa*.[7]

International trends in the proportions of bacterial isolates follow a similar route, differing by nation. There has been a significant increase in gram-positive isolates in India in recent years, in contrast with the decreasing trends in certain gram-positive strains observed in China.[8,9] In India, there has been a decrease in the overall prevalence of gram-negative organisms, which differs from the increasing trends in certain gram-negative strains observed in China and Taiwan.[8,9,13] Retrospective analyses conducted in Switzerland and South Korea indicate no difference in proportions of gram-positive and gram-negative organisms, as well as no discernible variation in causative pathogens responsible for microbial keratitis during their respective study periods.[10,12]

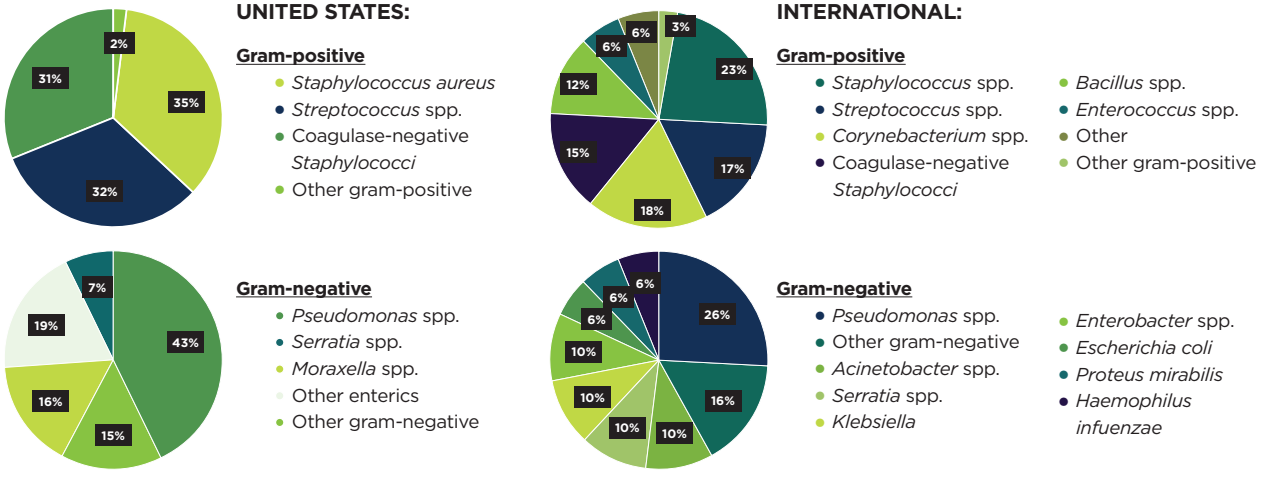
SUSCEPTIBILITY

Antibiotic sensitivity is a measure of the antibiotic concentration that will inhibit bacterial growth and is a predictor of the clinical response to antimicrobial treatment.[16] Techniques of bacterial culturing, such as natural agar plates and corneal scraping, are used to determine the bacteria in question and its sensitivity.[17] Knowledge of bacterial susceptibility can be helpful to guide the selection of antibiotics to achieve successful clinical outcomes.[18]

Retrospective analyses of gram-positive organisms conducted in the United States indicate significant variability in terms of antibiotic susceptibilities.[6,7] Gram-positive isolates demonstrate 100% susceptibility to vancomycin over time and are fairly sensitive to gentamicin, tetracycline and trimethoprim sulfamethoxazole.[6,7] However, susceptibility to fluoroquinolones, cefazolin and erythromycin is inconsistent.[6,7] Furthermore, researchers note a decrease in susceptibility of gram-positive organisms to levofloxacin and gentamicin over time.[6]

Analyses of gram-negative organisms indicated excellent *in vitro* susceptibility of *Pseudomonas* to fluoroquinolones and aminoglycosides.[6,7] Fluoroquinolones are also effective in *Serratia*, *Moraxella* and other enteric organisms.[6,7] Non-*Moraxella* gram-negative rods exhibit better *in vitro* sensitivity to ceftazidime than to moxifloxacin and tobramycin.[6]

Internationally, studies document differences in antibiotic sensitivities and trends between the various regions. Gram-positive isolates have a high susceptibility to vancomycin, fluoroquinolones (including levofloxacin, moxifloxacin and gatifloxacin), aminoglycosides (namely, erythromycin, gentamicin



Strain prevalence characteristics differ markedly between the United States and international regions (comprising India, China, Switzerland, Malaysia, South Korea, Taiwan, Spain, Colombia).

and tobramycin), chloramphenicol and impinemen.[8,9,12-15] In China, however, there has been a decrease in susceptibility of gram-positive isolates to levofloxacin, cefazolin, ceftazidime and chloramphenicol over time.[9] *Staphylococcus* species in particular have a high antibiotic sensitivity to vancomycin, teicoplanin and chloramphenicol and a low sensitivity to fluoroquinolones, such as ciprofloxacin.[8,13] Susceptibility of *Streptococcus pneumoniae* is highest to cefazolin and lowest to ciprofloxacin, which is mirrored by an overall trend of higher susceptibility of gram-positive cocci to cephalosporins relative to fluoroquinolones.[8,9]

In regard to gram-negative organisms, most are highly sensitive to fluoroquinolones (including ciprofloxacin and levofloxacin), aminoglycosides (namely gentamicin, amikacin and tobramycin), cephalosporins (including ceftazidime and cefepime) and carbapenem.[9,11-13] *Pseudomonas* species in particular demonstrate excellent *in vitro* sensitivity to fluoroquinolones, aminoglycosides and certain cephalosporins.[8,11-13]

Studies conducted in South Korea and Taiwan do not show significant changes in antibiotic sensitivity over time.[12,13] In comparison, analyses in China indicate a decreasing trend of susceptibilities. In China, fluoroquinolones were reported to be the most susceptible antibiotic to gram-negative *bacilli*, with an increased susceptibility to ofloxacin observed over time.[9]

ANTIBIOTIC RESISTANCE

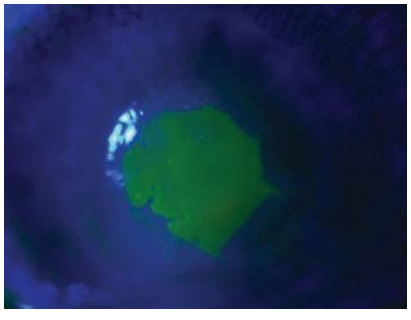
This occurs when bacteria acquire the ability to evade destruction by antibiotics through spontaneous mutation or horizontal gene transfer. Resistance is driven largely by overuse of antibiotics. The resistance process removes drug-sensitive bacteria and leaves resistant strains to proliferate. Causes of antibiotic resistance include the vast number of antibiotics prescribed, incorrect prescribing of antibiotics, extensive agricultural use of antibiotics and the lack of availability of new antibiotics on the market.[18] Trends in antibiotic resistance vary regionally, with certain bacterial organisms demonstrating increased resistance over time and other bacterial strains exhibiting no significant change in antibiotic resistance.

In the United States, trends in antibiotic resistance have changed over time and vary by region and bacterial strain. Resistance to moxifloxacin increases with each one-year increase in the culture date, and a trend of increasing resistance to gentamicin was observed among gram-positive organisms. Additionally, one study found the risk of culturing MRSA seems to increase with time in San Francisco, while no significant annual trends were noted in the proportions of oxacillin-resistant *Staphylococcus aureus* and oxacillin-resistant coagulase-negative *Staphylococci* in St. Louis.[6,7]

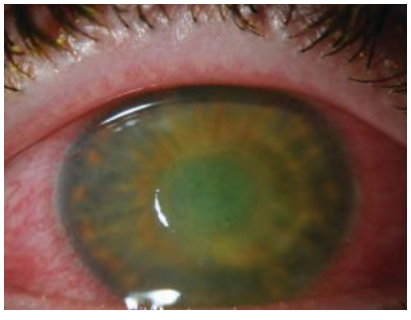
Analyses in Malaysia observe no increase in resistance rates for the commonly used antibiotics, although these findings do not hold true for other regions.[11] In Colombia, gram-negative organisms exhibit higher resistance rates overall, while in Taiwan, resistance is more common in gram-positive pathogens.[13,15] Similar to the United States, the risk of culturing MRSA in Taiwan increases with time.[13] This differs from findings in Spain and South Korea, where no trends have been observed for methicillin-resistant strains.[12,14] Furthermore, *Staphylococcus* species demonstrate a significant increase in the proportion resistant to oxacillin over time. This is in contrast to the pattern seen in the United States.[13] In Colombia and South Korea, moderate-to-high resistance is observed for gram-negative isolates to gentamicin, tobramycin, amikacin imipenem, gatifloxacin and ciprofloxacin, as well as for gram-positive isolates to Ciprofloxacin.[12,15]

TREATMENT STRATEGY

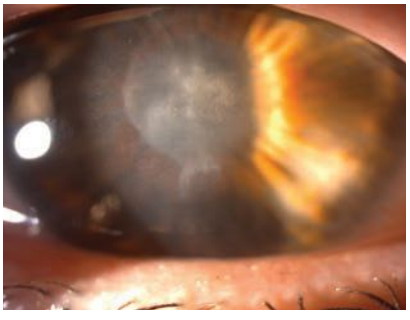
In addition to the current accepted methods used to treat microbial



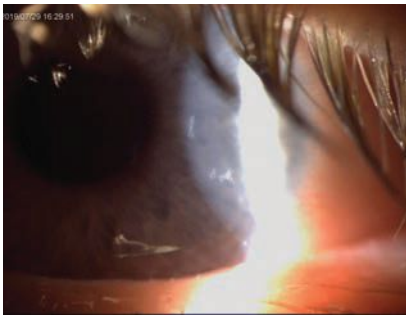
Fluorescein staining shows an active bacterial ulcer in a patient who slept in her contact lenses.



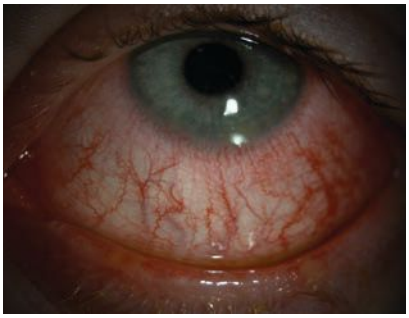
The patient's corneal ulcer is resolving.



She was left with this scar after her ulcer healed.



This patient had irregular epitheliopathy at presentation and ended up having an active bacterial infection secondary to contact lenses.



Hyperemia can be seen in this patient.

keratitis, a review of recent literature indicates several novel approaches may prove valuable for the treatment of bacterial corneal infections.

A broad-spectrum combination of polymyxin B–trimethoprim (PT) and rifampin demonstrated increased potency, improved antibiofilm activity and more rapid bactericidal activity compared with PT alone for the treatment of *Staphylococcus aureus* and *Pseudomonas* corneal infections.[19] This novel combination also exhibits a lower tendency to develop resistance than either individual agent or moxifloxacin.[19] Increased efficacy was also observed relative to commercial PT and moxifloxacin in murine models of keratitis.[19]

Thymosin beta-4 (Tβ4) is a naturally occurring amino acid protein that promotes wound healing and host defense and reduces corneal inflammation. Corneas treated with a combination of Tβ4 and ciprofloxacin to fight off keratitis caused by *Pseudomonas aeruginosa* demonstrate the most improvement in disease severity, with minimal impact on host immune response.[20]

Researchers investigated argon cold plasma as a potential treatment for therapy-resistant corneal infections, specifically for *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa*. Analyses indicate that argon cold plasma treatments can significantly reduce various corneal pathogens and improve vision post-treatment without damaging the ocular surface.[21]

In another study, patients with culture-positive bacterial keratitis—negative for fungal and protozoal species—received six or more daily drops of potent topical steroids, including prednisolone acetate 1%, phenylephrine hydrochloride 0.12%, dexamethasone 0.1% and prednisolone sodium phosphate 0.5%.[22] Patients on the high-dose steroid regimen have a 5.5-increased chance of better visual outcomes, although patients with *Nocardia* keratitis had poorer outcomes.[22] Treatment of bacterial keratitis with high-dose steroid regimens may prove to be an important clinical tool for improved visual outcomes after corneal infection.[22]

A working knowledge and understanding of common pathogens and their respective clinical therapies and current trends is essential to effectively manage bacterial keratitis and improve visual outcomes in patients. Given the widespread use of broad-spectrum antimicrobials and the subsequent emergence of antibiotic resistance, targeting various pathogens with treatments that have proven effective and using novel therapies adjunctively or in isolation may help improve success rates in the treatment of corneal ulcers and better preserve vision in those affected. RCCL

1. Bourcier T, Thomas F, Borderie V, et al. Bacterial keratitis: predisposing factors, clinical and microbiological review of 300 cases. Br J Ophthalmol. 2003;87(7):834-8.

2. Collier SA, Gronostaj MP, MacGurn AK, et al. Estimated burden of keratitis—United States, 2010. Morb Mortal Wkly Rep. 2014;63(45):1027-30.

3. Truong DT, Bui MT, Cavanagh HD. Epidemiology and outcome of microbial keratitis: private university versus urban public hospital care. Eye Cont Lens. 2018;44(Suppl 1):S82-6.

4. Acharya M, Farooqui JH, Jain S, et al. Pearls and paradigms in infective keratitis. Rom J Ophthalmol. 2019;63(2):119-27.

5. Odonkor ST, Addo KK. Bacteria resistance to antibiotics: recent trends and challenges. Int J Biol Med Res. 2011;2(4):1204-10.

6. Peng MY, Cevallos V, McLeod SD, et al. Bacterial keratitis: isolated organisms and antibiotic resistance patterns in San Francisco. Cornea. 2018;37(1):84-7.

7. Hsu HY, Ernst B, Schmidt EJ, et al. Laboratory results, epidemiologic features, and outcome analyses of microbial keratitis: a 15-year review from St. Louis. Am J Ophthalmol. 2019;198:54-62.

8. Das S, Samantaray R, Mallick A, et al. Types of organisms and in-vitro susceptibility of bacterial isolates from patients with microbial keratitis: a trend analysis of 8 years. Ind J Ophthalmol. 2019;67(1):49-53.

9. Lin L, Duan F, Yang Y, et al. Nine-year analysis of isolated pathogens and antibiotic susceptibilities of microbial keratitis from a large referral eye center in southern China. Infection and Drug Resistance. 2019;12:1295-302.

10. Bograd A, Seiler T, Droz S, et al. Bacterial and fungal keratitis: a retrospective analysis at a university hospital in Switzerland. Klin Monbl Augenheilkd. 2019;236(4):358-65.

11. Khor HG, Cho I, Lee KRCK, et al. Spectrum of microbial keratitis encountered in the tropics. Eye Cont Lens. 2019:1542-2321.

12. Mun Y, Kim MK, Oh JY. Ten-year analysis of microbiological profile and antibiotic sensitivity for bacterial keratitis in Korea. PLoS ONE. 2019;14(3):e0213103.

13. Liu HY, Chu HS, Wang IJ, et al. Microbial keratitis in Taiwan: a 20-year update. Am J Ophthalmol. 2019;205:74-81.

14. Tena D, Rodríguez N, Toribio L, et al. Infectious keratitis: microbiological review of 297 cases. Jpn J Infect Dis. 2019;72(2):121-3.

15. Galvis V, Parra MM, Tello A, et al. Antibiotic resistance profile in eye infections in a reference centre in Floridablanca, Colombia. Arch Soc Esp Oftalmol. 2019;94(1):4-11.

16. Smaill F. Antibiotic susceptibility and resistance testing: an overview. Can J Gastroenterol. 2000;14(10):871-5.

17. Leck A. Taking a corneal scrape and making a diagnosis. Comm Eye Health. 2009;22(71):42-3.

18. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. Pharm Therapeut. 2015;40(4):277-83.

19. Chojnacki M, Philbrick A, Wucher B, et al. Development of a broad-spectrum antimicrobial combination for the treatment of Staphylococcus aureus and Pseudomonas aeruginosa corneal infections. Antimicrob Agents Chemother. 2018;63(1):e01929-18.

20. Carion TW, Ebrahim AS, Kracht D, et al. Thymosin Beta-4 and ciprofloxacin adjunctive therapy improves Pseudomonas aeruginosa-induced keratitis. Cells. 2018;7(10):145.

21. Reitberger HH, Czugala M, Chow C, et al. Argon cold plasma—a novel tool to treat therapy-resistant corneal infections. Am J Ophthalmol. 2018;190:150-63.

22. Green M, Hughes I, Hogden J, et al. High-dose steroid treatment of bacterial keratitis. Cornea. 2019;38(2):135-40.

SMART STRATEGIES
for Using Antibiotics to Treat
CORNEAL INFECTION

Understand when to initiate appropriate therapy options.

By Fiza Shuja, OD, and Suzanne Sherman, OD

According to a recent study in *Cornea*, approximately one million annual ocular medical visits in the United States ended up with a bacterial keratitis diagnosis.[1,2] Of these patients, 76.5% received a prescription for antibiotics from their healthcare provider.[1,2]

The cost of treating bacterial keratitis is estimated to be around $377 million to $857 million per year.[3] Bacterial keratitis is only one cause of ocular infections, but it requires immediate intervention in order to prevent vision loss and minimize complications.

Viral and bacterial infections are the most common etiologies for bacterial keratitis. A proportion of 71,000 cases of severe infectious keratitis a year in America has been estimated, a lower proportion than non-infectious bacterial keratitis.[2,4]

To treat bacterial keratitis, practitioners initiate empirical therapy with broad-spectrum or fortified antibiotics prescriptions; however, overuse has led to a pattern of resistance that can cause difficulty in suitably managing the condition.[5]

This article explores the changes in trends regarding corneal infections and the situations where practitioners should use antibiotic treatment. Understanding common pathogens and effective treatments is essential in managing these patients with the most successful results.

BACTERIAL CONJUNCTIVITIS AND KERATITIS

Bacterial conjunctivitis is the second most common cause of conjunctivitis, and it is responsible for 50% to 75% of conjunctivitis cases in children.[6] Although conjunctivitis involves the conjunctiva specifically, it can affect the surrounding ocular structures that can lead to worsening infections, such as keratitis, which can become serious enough to cause blindness.[7]

In adults, a bacterial origin is less common than a viral one and is characterized by bacterial overgrowth, along with infiltration of the conjunctival epithelial layer. The origin can either be from direct contact with an infected individual's secretions or advanced through organisms colonizing within the patient's own nasal and sinus mucosa.[8]

Bacterial keratitis is an acute or chronic condition that can become sight-threatening if left untreated. These cases can lead to stromal inflammation and progressive tissue destruction, eventually causing perforation. It is commonly connected with risk factors that disturb the corneal epithelial integrity. Contact lens wear, trauma, impaired defense mechanism, immunosuppressive medication use and altered corneal surface structure postoperatively are all common predisposing factors.[8,9]

The most common risk factor in the US is contact lens wear. Microbial keratitis is approximately 15 times more likely in patients who sleep in their lenses and is positively correlated with the number of days patients wear their contact lenses without removal.[8] With the increase of contact lens wear gloally, bacterial keratitis has also increased accordingly.[9]

Bacterial conjunctivitis can be self-limiting and resolves on its own in one to two weeks due to

ABOUT THE AUTHORS

Dr. Shuja is an optometrist at New York–Presbyterian Hospital.

Dr. Sherman is an assistant professor of optometric sciences in ophthalmology and director of optometric services at the Columbia University Medical Center and an assistant attending at New York–Presbyterian Hospital.

the body's immune factors.[6] Gram-positive cocci and *Staphylococcus* species are known to inhabit skin cells, skin glands and mucous membranes. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a well-known gram positive cocci we always have to be on the lookout for. MRSA has a caused an increase of vancomycin use. *Propionibacterium acnes (P. acnes)* is one of the major causes of postoperative endophthalmitis but an uncommon cause of microbial keratitis.

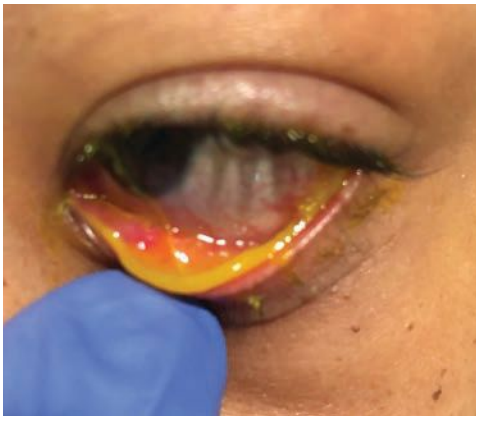
When caused by dangerous bacterial species, such as *Neisseria gonorrhoeae* or *Streptococcus pyogenes*, bacterial conjunctivitis can be serious and sight-threatening. In rare cases, it may foreshadow a life-threatening systemic disease, such as conjunctivitis caused by *Neisseria meningitidis*.[8]

The most common causative bacterial species are *Haemophilus influenza, Streptococcus pneumoniae, Staphylococcus aureus and Staphylococcus epidermidis* with staphylococci, specifically *S. aureus* and coagulase-negative *Staphylococci* (CoNS), reported most often.[7,10]

Several bacterial species simultaneously can cause most cases of acute bacterial conjunctivitis. This is why practitioners use broad-spectrum antibiotics as the first line of ophthalmic antibacterial treatment.[1] Antibiotics often accelerate clinical resolution and microbiological remission, while also lessening the risk of recurrence and the development of complications.[1]

Some prospective studies show that delaying antibiotic treatment until day three or four will reduce the use of unnecessary medications and not affect outcomes. The practitioner only initiated treatment if the signs were worsening, shortening the course and improving symptoms. These studies all advocate that initiation of antibiotics after day four provides finite benefits.[8]

Classic antibacterial options include tobramycin, trimethoprim, ciprofloxacin, gatifloxacin and moxifloxacin.[10] However, the widespread use of broad-spectrum antibiotics has resulted in resistance to those typical antibiotics.[10] Therefore, developing new antibiotics with high efficacy and safety against some resistant bacteria is necessary.[1]



This child has subcutaneous conjunctival membranes from a bacterial infection.

MANAGEMENT

The primary goal when dealing with corneal infections is always to prevent loss of sight and to preserve corneal clarity. It is safer to assume and, therefore, treat any presentation of microbial keratitis as bacterial keratitis for the best outcome.[9] However, it is difficult for the practitioner to quickly and effectively manage patients with presumed microbial conjunctivitis or keratitis. Although it would be ideal to have a confirmed definitive diagnosis before initiating therapy, bacterial pathogens can cause irreversible corneal scarring. It is therefore imperative to begin treatment before any damage occurs. The initiation of therapy must occur before an established diagnosis in order to prevent visual disability and limit the bacterial load.[8]

Preliminary therapy is comprised of empirical topical broad-spectrum antibiotics. For routine corneal ulcers, monotherapy of topical fluoroquinolones provides comparable therapy to combination therapy due to the enhanced penetration obtained with commercially available fluoroquinolones.[8] Fluoroquinolones can be instilled every 30 minutes to 60 minutes for a routine corneal ulcer.

If the ulcer is more severe, use a loading dose of every five minutes for 30 minutes to transfer

Classification of Bacterial Conjunctivitis[8]

Course of Onset	Severity	Common Organisms
Slow (days to weeks)	Mild to moderate	*Staphylococcus aureus* *Moraxella lacunata* *Proteus* spp. Enterobacteriaceae *Pseudomonas*
Acute or subacute (hours to days)	Moderate to severe	*Haemophilus influenzae* biotype III *Haemophilus influenzae* *Streptococcus pneumoniae* *Staphylococcus aureus*
Hyperacute (less than 24 hours)	Severe	*Neisseria gonorrhoeae* *Neisseria meningitidis*

therapeutic concentration to the stroma faster.[8]

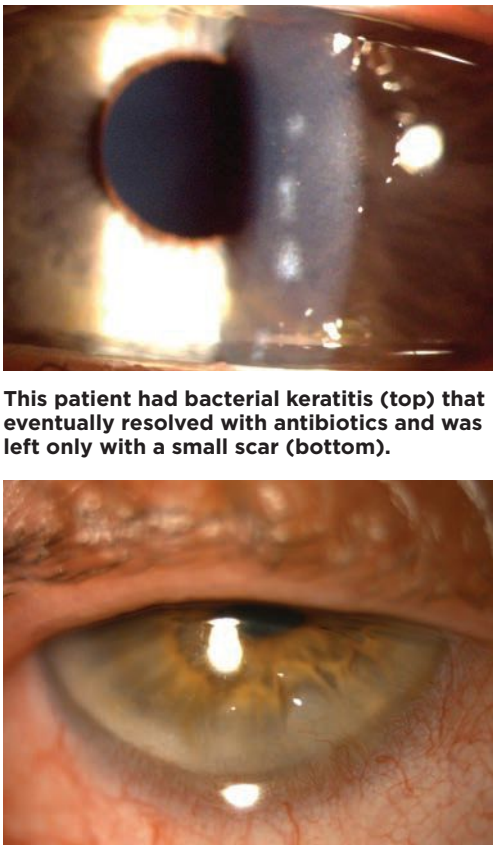
If monotherapy fails and/or the initial ulcer is large, central or atypical, consider combination therapies due to the additional gram-negative activity. In addition, if combination therapy fails or MRSA is suspected, initiate fortified antibiotics, including vancomycin. Fortified antibiotics are compounded at increased concentration. Remember that "fortifieds" can be difficult to obtain commercially and have greater corneal toxicity. According to a survey, the majority of corneal specialist respondents in the United States chose to treat corneal ulcers with fortified antibiotics, specifically vancomycin and tobramycin due to low antibiotic resistance, whereas a majority of international corneal specialists respondents chose fluoroquinolone treatment due to availability.[11]

Clinical parameters that can be helpful to monitor the response to antibiotic treatment include blunting the stromal infiltrate perimeter, decreased density of the stromal infiltrate, reduction of stromal edema and endothelial inflammatory plaque, reduction in anterior chamber inflammation, reepithelization and cessation of corneal thinning.[8]

In day-to-day clinical practice, we work side-by-side with anterior segment specialists in a tertiary care setting. Over the years, we have developed our own "smart" strategies for dealing with corneal infections.

1. Take a careful case history. Do not rely only on the information the patient gives you. Always ask about previous contact lens use, recent activities, surgeries, etc.
2. Ask about previous treatments. Many patients have already gone to a walk-in clinic or someone who is not an eye care provider. If they can't recall the exact medication given, ask about the cap color and dosage.
3. Conduct a careful slit lamp exam including lid eversion and fluorescein staining.
4. Use slit lamp photographs to compare images at each visit.
5. Perform IOP measurements and dilation are essential. If you haven't seen a patient recently, you cannot assume the posterior segment is not involved.

Once the presumed etiology is determined based on case history and clinical exam, personal experience shows it is most effective to use monotherapy of topical fluoroquinolones during the day and an added ointment at night. In the office, fourth generation fluoroquinolones are not always available; therefore, we give the patient a sample of the highest-generation drop available and a prescription for fourth generation fluoroquinolones to the pharmacy.



This patient had bacterial keratitis (top) that eventually resolved with antibiotics and was left only with a small scar (bottom).

Depending on the severity of the infection, it is helpful to space out follow-ups in order to give the antibiotics time to work and the cornea time to heal. At the follow-up, closely compare the current presentation to previous slit lamp photos. Oftentimes, clinical signs and patient symptoms will have started to improve before culture results have returned.

RISE OF THE RESISTANCE

Though bacterial keratitis requires treatment with antibiotics, it is crucial to understand how over-using and over-prescribing antibiotics can lead to resistance. Bacterial resistance to an antibiotic depends on the mechanism. The most common resistance mechanism, modification, can involve a mutation to the target site, making the

Common Causes of Bacterial Keratitis[8]

Common	Uncommon
Staphylococcus aureus *Staphylococcus epidermidis* *Streptococcus pneumoniae* *Pseudomonas aeruginosa* Enterobacteriaceae	*Neisseria spp.* *Moraxella spp.* *Mycobacterium spp.* *Nocardia spp.* Non–spore-forming anaerobes *Corynebacterium* spp.

drug ineffective.[12] Resistance can be coded into the bacterial genes and then passed between colonies and species, allowing it to spread quickly.[12]

Antibiotic resistance to penicillin can begin soon after the drug is introduced to treat infections.[13] Factors to blame for antibiotic resistance include over-prescribing, inappropriate dosing regimen, increased use of antibiotics in agriculture and increased exposure to systemic antibiotics.[14,15] When practitioners prescribe, a pattern of resistance can occur if patients are unable to self-administer properly or discontinue medications due to ocular discomfort from adverse effects.[15]

Many of the antibiotics treating the ocular surface are also used systemically for infections, except besifloxacin, which was formulated exclusively for ocular use to allow lower resistance rates.[14] We have seen some patients who believe they are cured and self-discontinue antibiotics early. Once this happened, the infection reappeared and the treatment course had to be resumed. It is therefore wise for optometrists to prevent over-prescribing and make sure the antibiotic treatment runs its course.

The increase in resistant bacteria over the years has led to studies, such as the Ocular Tracking Resistance in the United States Today (TRUST) and Antibiotic Resistance Monitoring in Ocular micRoorganisms (ARMOR) studies.[13,14] Ocular TRUST monitored *S. aureus*, *S. pneumoniae* and *H. influenzae* when treated with fluoroquinolones, macrolides, aminoglycosides, penicillin, dihydrofolate reductase inhibitors and polypeptides. Ocular TRUST studies reported 16.8% methicillin resistance from 2005 to 2006, which then increased to 50% by 2008.[16]

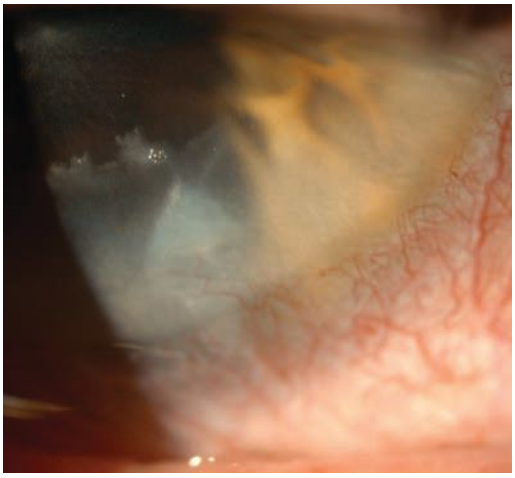
The ARMOR study monitors antibiotic resistance in ocular infections against *S. aureus*, CoNS, *S. pneumoniae*, *H. influenzae* and *P. aeruginosa*.[16] From 2009 to 2013, methicillin resistance was shown in staphylococcal isolates; however, it did not increase over the five years. Bacteria such as *S. pneumoniae* and *H. influenzae* were most susceptible to antibiotics, whereas there was multidrug resistance in 86.8% of methicillin-resistant *S. aureus* isolates and 77.3% of methicillin-resistant CoNS. The study also noted a higher number of methicillin-resistant staphylococcal infections in elderly patients.[16] *P. aeruginosa* and *H. influenzae* isolates showed low resistance against most of the antibiotics tested.

Most of the published data regarding ocular pathogens is collected from single centers; however, pathogens differ in prevalence geographically, reinforcing the need for studies like ARMOR, which are conducted nationwide in the United States. Understanding the location of bacteria can aid eye-care providers to target the more common pathogens—*S. aureus* is higher in the South and lower in the West, *S. pneumoniae* is higher in the Midwest and lower in the West and *P. aeruginosa* is higher in the Midwest and lower in the West.

Globally, antibiotic resistance continues to plague practitioners when treating keratitis. Moxifloxacin has shown increased resistance in India, despite its more "recent" foray in treating bacterial infections; there was low susceptibility of coagulase-negative *Staphylococcus* (61.2%) and methicillin-resistant *Staphylococcus* (53.1%) when treated with moxifloxacin. In the US, 26% of all organisms cultured were resistant

Antibiotic Smart Strategies

Routine Corneal Ulcer	Monotherapy: topical fluoroquinolones	• Equivalent to combination therapy	Every 30 to 60 minutes, tapered according to clinical response. More severe presentation: Loading dose every five minutes for 30 minutes.
	Second generation: ciprofloxacin, ofloxacin	• *Pseudomonas coverage* • Lack some gram-positive activity	
	Third and fourth generation: moxifloxacin, gatifloxacin, levofloxacin, besifloxacin	• Improved gram-positive activity • Atypical mycobacterial coverage • Limited activity against MRSA	
Monotherapy for initial ulcer, unless ulcer is large, vision-threatening or atypical	Combination therapy	• Active against gram-positive and gram-negative bacteria	
Failed monotherapy or combination therapy with large, vision-threatening, MRSA suspected	Fortified antibiotics	• Vancomycin gram +, greater coverage against MRSA	



Corneal scarring secondary to chronic blepharoconjunctivitis caused this case of keratitis.

to moxifloxacin, while 28% of *Staphylococcus aureus* bacterial isolates were resistant to ciprofloxacin or ofloxacin.[17]

ALTERNATIVE THERAPY

There are other treatment modalities to consider when treating bacterial keratitis. The use of steroids in treating bacterial keratitis remains a controversial issue. Early use of steroids can help reduce corneal stromal melt, neovascularization and corneal scarring that results from the inflammatory response against the infection. Instilling steroids in conjunction with fortified antibiotics can also help decrease discomfort. The counterargument is that steroids delay corneal healing, leading to a worse infection. Though steroid use leads to improvement for some patients, note that the use of steroids for fungal or *Acanthamoeba* infections can lead to terrible results, such as increased loss of vision or loss of the eye.

Studies have been performed to find new adjunct therapies to treat bacterial keratitis, especially with the rise of antibiotic resistance. Amniotic membranes, typically used during pterygium surgery, also help resolve epithelial defects and chemical injury. Amniotic membrane benefits include reepithelization by reinforcing basal epithelial cell adhesion, induction of epithelial cell migration, differentiation and proliferation of conjunctival and limbal epithelial progenitor cells, prevention of epithelial apoptosis and reduction of keratocyte apoptosis. Studies have shown improvement in epithelial defect, corneal haze and neovascularization when eyes were treated with amniotic membranes rather than antibiotics alone; however, larger studies needs to be conducted to analyze the full potential of amniotic membranes when treating bacterial keratitis.[18]

Treatment for corneal perforation with doxycycline has shown improvement in animal studies. In rabbit models, corneal perforation from *Pseudomonas* ulcers was reduced by 50% with systemic doxycycline use. Unfortunately, the lack of human studies makes it difficult to prove doxycycline as an effective therapy.

Collagen crosslinking, used to treat keratoconus, has antimicrobial properties and can potentially help resolve corneal ulcers from bacterial pathogens. Case reports have shown an improvement in symptoms and the resolution of treatment-resistant infections. Further trials and studies could help establish crosslinking as a viable treatment for those with antibiotic resistance and/or to prevent ocular toxicity.[19]

Though bacterial keratitis needs to be treated aggressively, exercise caution when using treating topical therapy options, such as steroids. Clinical assessment is imperative in making the correct diagnosis and managing it appropriately prevents vision loss. RCCL

1. Collier SA, Gronostaj MP, MacGurn AK, et al. Estimated burden of keratitis: United States, 2010. Morb Mortal Wkly Rep. 2014;63(45):1027-30.

2. Ballouz D, Maganti N, Tuohy M, et al. Medication burden for patients with bacterial keratitis. Cornea. 2019;38(8):933–7.

3. Smith AF, Waycaster C. Estimate of the direct and indirect annual cost of bacterial conjunctivitis in the United States. BMC Ophthalmol. 2009;9:13.

4. Jeng BH, Gritz DC, Kumar AB, et al. Epidemiology of ulcerative keratitis in Northern California. Arch Ophthalmol. 2010;128:1022–8.

5. Gokhale NS. Medical management approach to infectious keratitis. Indian J Ophthalmol. 2008;56(3):215-20.

6. Høvding G. Acute bacterial conjunctivitis. Acta Ophthalmol. 2008;86(1):5-17.

7. Teweldemedhin M, Gebreyesus H, Atsbaha AH, et al. Bacterial profile of ocular infections: a systematic review. BMC Ophthalmology. 2017;17:212.

8. American Academy of Ophthalmology. External disease and cornea: Basic and Clinical Science Course 2017-2018. 2017.

9. Wang JJ, Gao XY, Li HZ, Du SS. The efficacy and safety of besifloxacin for acute bacterial conjunctivitis: a Meta-analysis. Int J Ophthalmol. 2019;12(6):1027-36.

10. Al-Mujaini A, Al-Kharusi N, Thakral A, Wali UK. Bacterial keratitis: perspective on epidemiology, clinico-pathogenesis, diagnosis and treatment. Sultan Qaboos Univ Med J. 2009;9(2):184–95.

11. Austin A, Schallhorn J, Geske M, et al. Empirical treatment of bacterial keratitis: an international survey of corneal specialists. BMJ Open Ophthalmol. 2016;2:e00047.

12. Baum J, Barza M. The evolution of antibiotic therapy for bacterial conjunctivitis and keratitis: 1970-2000. Cornea. 2000;19(5):659-72.

13. McDonald M, Blondeau J. Emerging and antibiotic resistance in ocular infections and the role of fluoroquinolones. J Cataract Refract Surg. 2010;36(9):1588-98.

14. Thomas RK, Melton R, Asbell PA. Antibiotic resistance among ocular pathogens: current trends from the ARMOR surveillance study (2009-2016). Clin Optom (Auckl). 2019;11:15-26.

15. Samarawickrama C, Chan E, Daniell M. Rising fluoroquinolone resistance rates in corneal isolates: implications for the wider use of antibiotics within the community. Infection, Disease & Health. 2015;20:128-33.

16. Asbell PA, Sanfilippo CM, Pillar CM, et al. Antibiotic resistance trends from ocular pathogens in the US-cumulative results from the antibiotic resistance monitoring in ocular microorganisms (ARMOR) surveillance study. US Ophthalmic Review. 2017;10(1):35-8.

17. Ung L, Bispo PJM, Shanbhag SS, et. al. The persistent dilemma of microbial keratitis: global burden, diagnosis, and antimicrobial resistance. Surv Ophthalmol. 2019;64:255-71

18. Dakhil TAB, Stone DU, Gritz DC. Adjunctive therapies for bacterial keratitis. Middle East Afr J Ophthalmol. 2017;24(1):11–7.

19. Austin A, Lietman T, Rose-Nussbaumer J. Update on the management of infectious keratitis. Ophthalmology. 2017;124(11):1678–89.

Earn up to 18-28 CE Credits*

NEW TECHNOLOGIES & TREATMENTS IN EYE CARE 2020 REVIEW EDUCATION GROUP

Join us for our

2020 MEETINGS

FEBRUARY 14-17, 2020 - ASPEN, CO

Annual Winter Ophthalmic Conference
Westin Snowmass Conference Center
Program Co-chairs: Murray Fingeret, OD, FAAO and Leo P. Semes, OD, FACMO, FAAO
REGISTER ONLINE: www.skivision.com

APRIL 16-19, 2020 - AUSTIN, TX

Omni Barton Creek
Joint Meeting with OCCRS**
Program Chair: Paul M. Karpecki, OD, FAAO
REGISTER ONLINE: www.reviewsce.com/austin2020

MAY 29-31, 2020 - SAN DIEGO, CA

Manchester Grand Hyatt
Program Chair: Paul M. Karpecki, OD, FAAO
REGISTER ONLINE: www.reviewsce.com/sandiego2020

JUNE 5-7, 2020 - ORLANDO, FL

Disney Yacht & Beach Club
Program Chair: Paul M. Karpecki, OD, FAAO
REGISTER ONLINE: www.reviewsce.com/orlando2020

NOVEMBER 6-8, 2020 - PHILADELPHIA, PA

Philadelphia Marriott Downtown
Program Chair: Paul M. Karpecki, OD, FAAO
REGISTER ONLINE: www.reviewsce.com/philadelphia2020

Visit our website for the latest information: www.reviewsce.com/events
e-mail: reviewmeetings@jhihealth.com or call: 866-658-1772

Administered by: REVIEW EDUCATION GROUP

Medscape LIVE!

COPE *Approval pending

SALUS UNIVERSITY Pennsylvania College of Optometry

OCCRS **17th Annual Education Symposium Joint Meeting with NT&T in Eye Care

Review Education Group partners with Salus University for those ODs who are licensed in states that require university credit.
See www.reviewsce.com/events for any meeting schedule changes or updates.

TAKE ON Neurotrophic Keratitis With These Clinical Tools

The more it progresses, the more challenging it becomes, so **early detection** and **diagnosis** are key.

By Megan Mannen, OD

Neurotrophic keratitis (NK) is a potentially sight-threatening condition marked by decreased or absent corneal sensation. The condition is caused by damage both to the trigeminal nerve along its corneal distribution and at any point in the pathway from the ganglion to the basal plexus. This damage compromises corneal integrity by altering the metabolism and mitosis processes of the corneal epithelium, which results in reduced innate immunity of the ocular surface and delayed healing.[1,2] If allowed to progress, damage could advance to the point of ulceration and, in severe cases, corneal perforation.[1-3]

NK is easy to manage early on in the disease process but remains one of the most challenging corneal conditions to treat in its severe stages. This article will review the causes, diagnostic findings and treatments available for NK throughout all stages of disease.

TRACE IT TO THE SOURCE

The most common etiologies of NK are herpes simplex virus (HSV) and varicella zoster virus (VZV).[1] Among herpes viruses, zoster causes more severe neurotrophy, as it may inflict damage both centrally at the ganglion and peripherally at the basal plexus. Alternatively, HSV only causes peripheral nerve damage. Patients suffering from herpes zoster ophthalmicus experience shorter corneal nerve length and lower corneal nerve count.[4] The zoster virus lies dormant in the trigeminal ganglion, and when it reactivates along the nasociliary distribution, it results in corneal compromise.[4] In both HSV and VZV, these damaging effects occur quickly and have long-lasting impacts on the integrity of the corneal epithelium.

Beyond viral eye disease, there are a variety of other causes of NK, including repeated corneal surgeries, chemical burns, contact lens abuse, medications, tumors and surgical complications resulting in trigeminal nerve palsies.[1,5]

Systemic disorders such as diabetes also contribute to NK. The longer a patient has diabetes, the more severe their corneal nerve damage might be. This manifests in diminished corneal tissue sensation similar to that occurring with peripheral neuropathy. Additionally, peripheral treatment with panretinal photocoagulation for proliferative diabetic retinopathy worsens the degree of neurotrophy.[5] In fact, corneal confocal microscopy has been shown to be useful in the early diagnosis of peripheral neuropathy due to its ability to detect subtle reductions in corneal nerve density and length.[6] This form of microscopy can assess small nerve fibers, which neuropathy affects first.[6] Because of the link between diabetic neuropathy and corneal integrity, consider the role of underlying neurotrophy in patients with diabetes and other ocular surface disease.

Regardless of its specific source, corneal neurotrophy is typically not associated with pain or discomfort due to the lack of sensation it is accompanied by. These patients will, however, likely report reduced vision, especially as the condition becomes more severe. Medicamentosa is a potential cause of corneal neurotrophy that should always be considered

ABOUT THE AUTHOR

Dr. Mannen practices at a private optometry and ophthalmology clinic in the greater Ogden, Utah area. She completed her residency at the Walla Walla Veteran Affairs Medical Center and Pacific Cataract and Laser Institute. She is also a fellow of the American Academy of Optometry.

as a differential and managed appropriately. Topical medications most likely to have noxious ocular surface effects include anesthetics, beta-blockers and non-steroidal anti-inflammatories (NSAIDs). Most of these medications use benzalkonium chloride as the preservative.[7] Monitor the ocular surface closely in glaucoma patients using beta-blockers and in post-surgical patients using NSAIDs, as these are the medications most commonly prescribed to these patients.

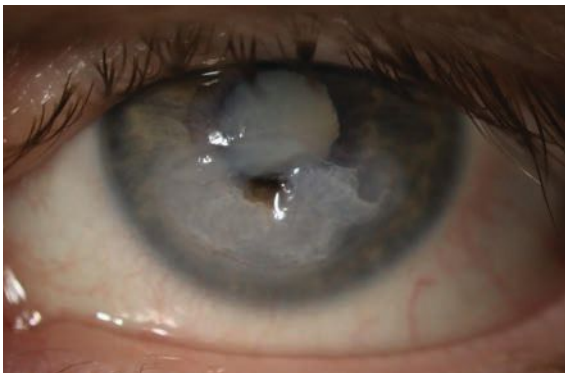


Fig. 1. A 51-year-old Caucasian female presented with progressively worsening vision in the left eye over the last two months but no more discomfort. She reported using bacitracin-Polymyxin B-neomycin-hydrocortisone ophthalmic solution TID and diclofenac BID for approximately two months while in the hospital.

Using a greater number of medications further increases the risk of toxicity.[7] If topical toxicity is suspected, discontinue medications and monitor the cornea for improvement. Systemic medications have also been shown to perpetuate corneal neurotrophy. These include antihistamines, neuroleptics and antipsychotics.[2] Consult primary care providers and consider drug cessation if these mediations are contributing to corneal compromise.

THE THREE STAGES OF NK

There are three traditional clinical stages of NK. The first involves tear dynamic alteration, punctate epithelial erosion, superficial neovascularization and stromal scarring. These findings are common and can be mistaken for other ocular surface diseases, but decreased corneal sensation, lack of symptoms and patient history will help with the diagnosis.[1,2,8]

The second stage of NK is marked by a persistent epithelial defect. The defect may be surrounded by a loose, edematous or boggy epithelium. Stromal edema and folds in Descemet's membrane may also accompany these clinical signs. Cells and flare, which may occasionally worsen into a sterile hypopyon, are often present in this stage and can make the differentiation between microbial keratitis and neurotrophic disease more challenging.[1,2,5,8]

The third and final stage of neurotrophy involves corneal stroma ulceration. This is defined as an epithelial break with underlying stromal inflammation. The stroma is made up of organized collagen fibers called lamellae. Once the stroma is penetrated, the collagen fibrils start to degrade. This damage attracts white blood cells, which infiltrate the damaged tissue. These immune cells proceed to release matrix metalloproteinases (MMPs) and oxygen radicals, which are pro-inflammatory and cause the stroma to progressively degrade.[9] This may lead to corneal melt and perforation—an ocular emergency that requires immediate attention and treatment to best preserve vision and globe integrity.[1,2,8]

CLINICAL DIAGNOSIS

Diagnosing NK involves evaluating corneal sensation. Corneal aesthesia can be tested using a few different methods. Cotton wisps and (non-flavored) dental floss are used most frequently, as they are inexpensive and readily available.

Approach the unaffected eye first and test it in quadrants and centrally. Then, proceed to the other eye and test the same zones, allowing the patient to grade the sensitivity in comparison with its counterpart.

Relative neurotrophy is gradable using both subjective responses and observable differences in patient blink force and recoil. For consistency, use a near uniform length of wisp or floss each time you test (~3cm is standard) to ensure equal force is applied with each touch. Alternatively, the Cochet-Bonnet esthesiometer is a more repeatable and quantifiable test of aesthesia. It records a patient's response to contact with a nylon line on a scale between 0cm and 6cm.[10] A lower reading indicates more reduced corneal sensitivity.[11]

TREATMENT STRATEGY

Treatment of NK is based on disease etiology and severity. In stage one, optimizing the ocular surface is the primary goal. Preservative-free artificial tears, punctal occlusion and Restasis (Allergan) or Xiidra (Novartis) are frequently prescribed to improve tear volume. Comorbidities, such as meibomian gland dysfunction, exposure keratitis and limbal deficiency, should also be addressed to prevent further corneal damage.

When NK progresses to stage two, closure of the defect and prevention of progressive stromal thinning are the primary objectives. Use scleral lenses, bandage soft contact lenses and amniotic

membranes in attempts to close the epithelial defect. Scleral lenses can act as a moisture chamber to offer a fluid reservoir and buffer against the mechanical force of the blink. Bandage contact lenses provide a short-term barrier to lid friction. Amniotic membranes contain placental tissue and, thus, a variety of growth factors. They have been shown to increase corneal epithelialization, promote tissue repair and heal persistent epithelial defects.[12] Additionally, they decrease MMPs, which normally reduce tissue growth and turnover and, thus, inflammation.[13] Each of these therapies should be combined with antimicrobial prophylaxis to prevent bacterial super-infection.

Consider a temporary lateral tarsorrhaphy to heal persistent defects. A temporary tarsorrhaphy joins the eyelids together with three or four sutures. Wait until the wound resolves to release the tarsorrhaphy, as premature suture removal makes these epithelial defects more likely to recur.[8,14] Two alternatives to a tarsorrhaphy are a Botox injection into the levator to create a temporary ptosis and palpebral spring use.[8,15] These surgical interventions may be helpful in cases of pure exposure keratopathy as well.

Serum-based eye drops are becoming more widely used therapies for stages one and two of NK. These drops are created from blood samples, which are clotted, centrifuged and diluted with either sterile saline or a balanced salt solution.[16] All dilution preparations have proved useful in resolving persistent epithelial defects.[17] Additionally, umbilical cord serum, substance P with insulin-like growth factor 1 and nerve growth factor drops are being explored as future mainstream NK treatments due to their ability to repair nerve damage.[2,8,11,18,19] In fact, Oxervate (Dompé)—a recombinant human nerve growth factor—was recently FDA-approved for the treatment of NK. Treatment includes six daily drops over an eight-week course and has shown extremely promising results in repairing persistent corneal defects.[20] Nerve growth factor promotes epithelial healing and increases corneal sensitivity.[21,22]

Also gaining popularity is corneal neurotization, which restores corneal sensation by transferring healthy nerve tissue to the limbus of the affected cornea. It is most commonly performed on the distal ends of the supratrocheal and supraorbital nerves.[23,24] The donor nerve is drawn together with the damaged nerve with the hope of regenerating corneal sensation, which could take up to six months following surgery.[23] Although neurotization procedures are extensive, the least invasive techniques use cadaver nerve tissue or endoscopy.[23] Neurotization is thought to lead to direct nerve sprouting and provide a potential cure to NK.[23]

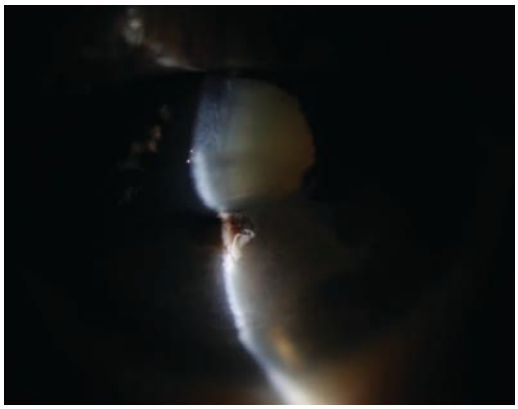


Fig. 2. Slit lamp exam revealed a perforated corneal ulcer involving the inferior visual axis with a collapsed anterior chamber and iris prolapse in the left eye.

Topical steroids may be helpful in managing neurotrophy caused by chemical burns; however, due to their immunosuppression and delayed healing effects, they are considered controversial in treating pure NK. Further, they have been found to increase the risk of corneal melting and perforation by up-regulating collagenases, which leads to enhanced stromal breakdown. In an effort to prevent this, avoid steroids if possible.[1,2,25] If a steroid is necessary, pair it with an appropriate antibiotic to keep normal flora from infecting the NK.

Stage three of NK is characterized by a sterile ulceration or melting of the stroma with the potential to perforate. It is promoted by the prolonged presence of epithelial defects. Collagenase activity is up-regulated by the presence of these chronic epithelial defects. This leads to thinning of the stroma with subsequent scarring and warpage of the cornea if re-epithelialization occurs or, worse— in the absence of re-epithelialization—if progression to perforation takes place.[5]

While steroids are generally avoided due to their ability to potentiate collagenase activity, medications that down-regulate these enzymes can be helpful by decreasing potentiators of melt. These include N-acetylcysteine, oral tetracycline antibiotics and medroxyprogresterone.[1,9,25]

If perforation is impending or has already occurred, treatment takes on a new level of urgency. Treatments include cyanoacrylate glue or fibrin adhesive application and amniotic membrane transplantation as temporizing measures. Adhesive options are ther-

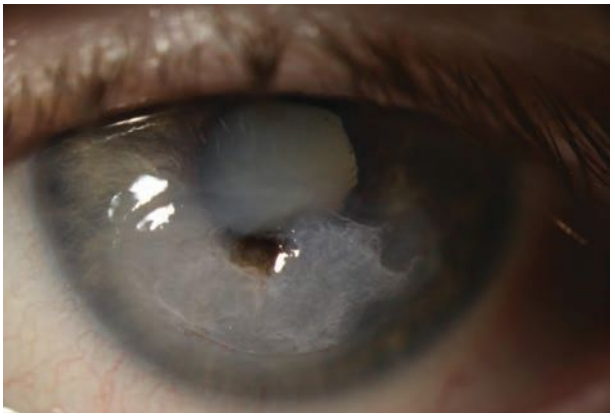


Fig. 3. The patient underwent emergency penetrating keratoplasty (PK) followed by a repeat PK with cataract extraction. The culture performed prior to the first corneal transplant was negative for microbial growth. Due to a persistent epithelial defect following PK, she needed multiple Prokera (Bio-Tissue) membranes, tarsorrhaphy and an amniotic membrane transplant. Post-op visual acuity was 20/400 with pinhole acuity ranging from 20/80 to 20/200.

apeutic via tectonic improvement and polymorphonuclear leukocyte reduction, which arrests stromal lysis via the inhibition of collagenases.[15,25,26] If ulceration continues to worsen, follow this step with a more definitive conjunctival flap or keratoplasty.

Conjunctival flaps are a definitive treatment for neurotrophy but come at a significant burden to visual potential. They promote healing by providing fibrovascular tissue rich in growth factors. The primary goal is to preserve globe integrity. Conjunctival tissue is not susceptible to the same mechanisms that lead to neurotrophic disease and, thus, the potential for perforation is eliminated. Flaps are reserved for chronic ulcers with poor visual prognoses because although the conjunctival flap tissue thins, it remains vascularized, limiting best-corrected visual acuity.[14]

Once neurotrophy advances to perforation, treatment depends largely on size. Small perforations can be glued, while large perforations are generally repaired with patch grafts or penetrating keratoplasties. A penetrating keratoplasty is a full-thickness transplant—the graft type used in most NK cases that lead to perforation. Transplants have a better chance of survival if they can be delayed with temporizing measures.[13,27] This allows time for inflammation to subside. Unfortunately, corneal transplants in neurotrophic patients are more likely to fail due to a propensity for continued or even worsening neurotrophy, which leads to chronic, non-healing epithelial defects.[5]

The prognosis of NK depends largely on severity, duration and comorbidities. Severely neurotrophic corneas are among the most difficult corneal pathologies to effectively manage, as sight is threatened and the potential for recurrence is high. The primary objectives for appropriate management should be to optimize the ocular surface, close epithelial defects and reduce collagenase activity. Careful attention to the many facets of neurotrophy should be given to provide optimal patient care, maintain ocular integrity and ultimately preserve vision. RCCL

1. Bonini S, Rama P, Olzi D, et al. Neurotrophic keratitis. Eye (Lond). 2003:17(8):989-95.

2. Semeraro F, Forbice E, Romano V, et al. Neurotrophic keratitis. Ophthalmologica. 2014:231(4):191-7.

3. Srinivasan S, Lyall DAM. Clinical Gate. Neurotrophic keratopathy. clinicalgate.com/neurotrophic-keratopathy/. August 3, 2015.

4. Hamrah P, Cruzat A, Dastjerdi MH, et al. Unilateral herpes zoster ophthalmicus results in bilateral corneal nerve alteration: an in vivo confocal microscopy study. Ophthalmology. 2013;120(1):40-7.

5. Chang BH, Groos EB. Neurotrophic keratitis. In: Cornea: Fundamentals, Diagnosis, and Management. Elsevier; 2017:1035-42.

6. Petropoulos IN, Alam U, Fadavi H, et al. Rapid automated diagnosis of diabetic peripheral neuropathy with in vivo corneal confocal microscopy. Invest Ophthalmol Vis Sci. 2014;55(4):2071-8.

7. Okoro CC, Amiebenomo OM, Aruotu N. Medicamentosa keratoconjunctivitis: a case report. Afr Vis Eye Health. 2016;75(1).

8. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;8:571-9.

9. Ralph RA. Tetracyclines and the treatment of corneal stromal ulceration: a review. Cornea. 2000;19(3):274-7.

10. Lambiase A, Rama P, Aloe L, et al. Management of neurotrophic keratopathy. Curr Opin Ophthalmol. 1999;10(4):270-6.

11. Yoon KC, You IC, Im SK, et al. Application of umbilical cord serum eyedrops for the treatment of neurotrophic keratitis. Ophthalmology. 2007;114(9):1637-42.

12. Kaufman SC. Anterior segment complications of herpes zoster ophthalmicus. Ophthalmology. 2008;115(2 Suppl):S24-32.

13. Solomon A, Meller D, Prabhasawat P, et al. Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. Ophthalmology. 2002;109(4):694-703.

14. Mantelli F, Nardella C, Tiberi E, et al. Congenital corneal anesthesia and neurotrophic keratitis: diagnosis and management. Biomed Res Int. 2015;2015:805876.

15. Portnoy SL, Insler MS, Kaufman HE. Surgical management of corneal ulceration and perforation. Surv Ophthalmol. 1989;34(1):47-58.

16. Shaheen BS, Bakir M, Jain S. Corneal nerves in health and disease. Surv Ophthalmol. 2014;59(3):263-85.

17. Jeng BH, Dupps WJ Jr. Autologous serum 50% eyedrops in the treatment of persistent corneal epithelial defects. Cornea. 2009;28(10):1104-8.

18. Chikama T, Fukuda K, Morishige N, et al. Treatment of neurotrophic keratopathy with substance-P-derived peptide (FGLM) and insulin-like growth factor I. Lancet. 1998;351(9118):1783-4.

19. Yanai R, Nishida T, Chikama T, et al. Potential new modes of treatment of neurotrophic keratopathy. Cornea. 2015;34(Suppl 11):S121-7.

20. Bonini S, Lambiase A, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology. 2018;125(9):1332-43.

21. Bonini S, Lambiase A, Rama P, et al. Topical treatment with nerve growth factor for neurotrophic keratitis. Ophthalmology. 2000;107(7):1347-51.

22. Lambiase A, Rama P, Bonini S, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med. 1998;338(17):1174-80.

23. Koaik M, Baig K. Corneal neurotization. Curr Opin Ophthalmol. 2019;30(4):292-8.

24. Terzis JK, Dryer MM, Bodner BI. Corneal neurotization: a novel solution to neurotrophic keratopathy. Plast Reconstr Surg. 2009;123(1):112-20.

25. Jhanji V, Young AL, Mehta JS, et al. Management of corneal perforation. Surv Ophthalmol. 2011;56(6):522-38.

26. Setlik DE, Seldomridge DL, Adelman RA, et al. The effectiveness of isobutyl cyanoacrylate tissue adhesive for the treatment of corneal perforations. Am J Ophthalmol. 2005;140(5):920-1.

27. Nurözler AB, Salvarli S, Budak K, et al. Results of therapeutic penetrating keratoplasty. Jpn J Ophthalmol. 2004;48(4):368-71.

1 CE Credit
(COPE APPROVED)

Unlocking the Mystery of Corneal Dystrophies

Optometrists are often the first to detect the clues and sleuth out the diagnosis. Here's what to look for. By Mitch Ibach, OD, and Larae Zimprich, OD

Corneal dystrophies are a group of progressive inheritable conditions that, over time, cause bilateral pathology. The manifestations, which are commonly deposits of material in the anterior cornea and cell atrophy in the posterior cornea, are not associated with trauma, infection or inflammation; rather, they are secondary to genetic mutations.[1]

Although corneal dystrophy is a rare condition, the familial impact makes diagnosis and appropriate counseling of the utmost importance.

This review aims to unlock the mystery of corneal dystrophies by discussing prevalence, genetic patterns, slit lamp clues, treatments and other pertinent points to help clinicians better diagnose and care for these patients.

Classification of corneal dystrophies is routinely based on the affected corneal layer. A recent epidemiologic retrospective analysis of managed care patients revealed a prevalence of a single corneal dystrophy at 0.13%.[1] Endothelial dystrophies were the most common (60.4% of the total) followed by anterior dystrophies (15.6%). Lastly, stromal dystrophies were identified as the least frequent.[1] However, 26% of cases in this study were listed as "unspecified" dystrophies.

ANTERIOR CORNEAL DYSTROPHIES

Four main corneal dystrophies affect the superficial cornea: epithelial basement membrane dystrophy (EBMD), Meesmann dystrophy, Reis-Bucklers dystrophy and Thiel-Behnke dystrophy. The epithelium, approximately 50µm thick, serves as a barrier to provide protection and allow the diffusion of oxygen from the tear film. All of these dystrophies can compromise the epithelium, which often leads to pain and irregular astigmatism, which causes poor visual outcomes.

Epithelial basement membrane dystrophy. EBMD is a bilateral, though often asymmetric, condition characterized by thickening and redundancy of the corneal epithelial basement membrane and the abnormal adhesion to the basal epithelial cells. It is not uncommon for patients to be asymptomatic or even unaware they have the condition.

There are reported cases of EBMD with studied point mutations in the TGFβI gene on chromosome 5 in an autosomal dominant pattern; however, some feel that it is more of a degeneration rather than a true dystrophy.[2] The genetic inheritance pattern is rather weak, which leads some people to believe it is a degeneration associated with aging, dry eye and trauma.

Patients who are symptomatic may complain of blurred vision due to induced irregular astigmatism, mild to severe pain, sensitivity to light, tearing or a gritty, sandy-like feeling. Oftentimes, a patient's symptoms can be exacerbated upon awakening due to the detachment of damaged epithelium, which may cause significant pain. Once this occurs, the cornea may become prone to recurrent corneal erosion (RCE). Approximately 10% of patients with EBMD experience recurrent corneal erosions and, conversely, 50% of patients with RCE evidence EBMD in the contralateral eye.[3]

Although EBMD is one of the most common corneal dystrophies, it may present in a variety of ways. Slit-lamp examination of a patient with EBMD may reveal bilateral subepithelial microcysts, chalky patches, thickened gray areas that resemble fingerprints or map-like lesions—giving us the term "map-dot-fingerprint" dys-

ABOUT THE AUTHORS

Dr. Ibach is a residency-trained optometrist at Vance Thompson Vision in Sioux Falls, SD. He specializes in anterior segment surgical care, including cataracts, corneal diseases, glaucoma and refractive surgeries.

Dr. Zimprich is the current optometry resident at Vance Thompson Vision, where she will specialize in ocular disease as well as comanagement of refractive, cataract, corneal and glaucoma surgeries. She recently graduated from Massachusetts College of Pharmacy and Health Sciences.

trophy. These findings are confined to the epithelial layer, and negative staining in a whorl-like pattern can be observed with the instillation of fluorescein.

Meesmann dystrophy. This is an autosomal-dominant epithelial corneal dystrophy. Meesmann dystrophy typically manifests from a young age and is caused by a defect in the KRTI2 gene, which leads to thickening of the epithelial basement membrane, similarly to EBMD.[4] However, slit-lamp examination reveals bilateral, small, punctate or bubble-like intraepithelial cysts concentrated in the interpalpebral region.

Reis-Bucklers and Thiel-Behnke dystrophies. These are Bowman's layer dystrophies caused by mutations in TGFβI that manifest later in life compared with Meesmann corneal dystrophy.[4] Corneal examination in a patient with Reis-Bucklers or Thiel-Behnke dystrophy may reveal subepithelial deposits of hyaline-like material that damage and eventually replace Bowman's layer.[2] The cornea may also show dense gray-white subepithelial opacities centrally that worsen with age.

Although clinically similar, they can be differentiated from one another by the characteristic finding of curled filaments within Bowman's membrane on confocal microscopy, which is pathognomonic for Thiel-Behnke.[4]

RCEs may occur in all epithelial and Bowman's dystrophies due to ruptured cysts and an unstable epithelium; however, they are more common in Reis-Bucklers and Thiel-Behnke dystrophies.[4] Otherwise, typical symptoms such as glare, light sensitivity and blurred vision are generally mild.

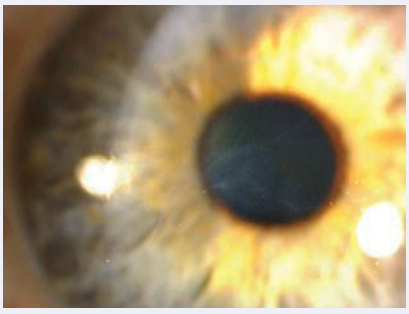
TREATMENT OF ANTERIOR DYSTROPHIES

The primary therapy goal in patients with epithelial basement membrane or Bowman's dystrophies is to maintain the integrity of the ocular surface.

A patient who is mildly symptomatic may be managed conservatively with lubrication. If symptoms worsen, medical treatments such as punctal plugs, hyperosmotic agents and topical or oral anti-inflammatories can be added. Although not a cure, patients can be fit in scleral lenses. These lenses completely vault over the cornea to protect the fragile epithelium while correcting vision compromised by irregular astigmatism.

The treatment of RCEs is tailored toward restoring the epithelium and decreasing patient pain, so placement of a bandage contact lens or amniotic membrane on the cornea is common. For any patient with an epithelial defect wearing a bandage lens, add a topical antibiotic for infection prophylaxis. Topical and/or oral anti-inflammatories can decrease matrix-metalloproteinase-9 (MMP-9) as well as speed up healing and prevent recurrent erosions. In a small study of seven patients

Central epithelial basement membrane dystrophy on high magnification.



EBMD in a patient with a history of fingernail trauma.

Release Date: November 15, 2019
Expiration Date: November 15, 2022
Estimated time to complete activity: 1 hour

Jointly provided by Postgraduate Institute for Medicine and Review Education Group.

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Educational Objectives: *After completing this activity, the participant should be better able to:*

- Identify the most common traits as well as the characteristic signs and symptoms related to corneal dystrophies.
- Consider the differential diagnosis for corneal dystrophies.
- Perform the necessary elements of the patient history, ocular examination/vision testing and laboratory testing required to diagnose corneal dystrophies.
- Distinguish the different types of corneal dystrophies most commonly encountered by optometrists, with at least a cursory understanding of their genetic inheritance.
- Provide, or otherwise obtain, the ocular and systemic treatment that the patient requires.

Target Audience: This activity is intended for optometrists engaged in the care of patients with corneal dystrophies.

Accreditation Statement: In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Review Education Group. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education, the Accreditation Council for Pharmacy Education, and the American Nurses Credentialing Center, to provide continuing education for the healthcare team. Postgraduate Institute for Medicine is accredited by COPE to provide continuing education to optometrists.

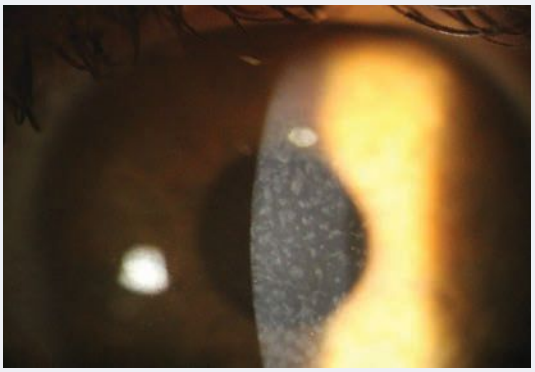
Faculty/Editorial Board: Mitch Ibach, OD, Vance Thompson Vision, Sioux Falls, SD, and Larae Zimprich, OD, Vance Thompson Vision.

Credit Statement: This course is COPE approved for 1 hour of CE credit. Course ID is **65002-AS**. Check with your local state licensing board to see if this counts toward your CE requirement for relicensure.

Disclosure Statements:
Dr. Ibach receives consulting fees from Aerie, Alcon, Avedro, Glaukos, Ocular Therapeutix and fees for non-CME/CE services from Aerie and Glaukos; and has ownership interest in Equinox.
Dr. Zimprich has no disclosures.
Managers and Editorial Staff: The PIM planners and managers have nothing to disclose. The Review Education Group planners, managers and editorial staff have nothing to disclose.

with traumatic RCEs who were treated with a combination of topical steroid and oral doxycycline, all patients' epithelial defects healed in 10 days or less with no recurrence of erosion for at least three months.[5]

All of these treatments support the stability of the ocular surface, but they won't cure the condition. A more permanent approach is surgical intervention. Superficial keratectomy, where the epithelium is debrided with or without excimer laser phototherapeutic keratectomy (PTK), may be considered for superficial abnormalities of the cornea. These can be used to polish corneal irregularities or opacities within the anterior 10% to 20% of the cornea.[6]



Reis-Bucklers dystrophy with central grayish opacities in Bowman's layer.

STROMAL DYSTROPHIES

The stroma represents the thickest layer of the cornea, measuring about 450µm. It is made up of dense, regular connective tissue that contains keratocytes, collagen, ground substance and water. Stromal dystrophies reside deep within the cornea and are typically treated in a conservative manner; but if stromal opacification presents, treatment options are limited.

Multiple stromal dystrophies can affect the cornea, but the most common are macular dystrophy, granular dystrophy, lattice dystrophy, Avellino dystrophy and Schnyder dystrophy.

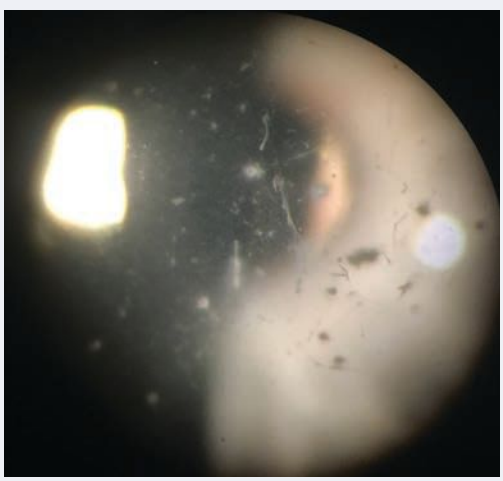
Macular corneal dystrophy (MCD). This is the least common yet the most visually impairing stromal dystrophy. Despite its classification, MCD can also affect Descemet's membrane and the endothelium. Caused by mutations in the CHST6 gene, MCD is the only autosomal recessive stromal dystrophy and is associated with an aggregation of glycosaminoglycans and mucopolysaccharides within the stroma.[4]

In affected patients, the cornea demonstrates bilateral corneal opacities that extend throughout the thickness of the stroma. A key slit-lamp differentiator for MCD is that the stromal opacities commonly extend out to the limbus. As the condition progresses, the opacities coalesce and guttata can develop within the endothelium, both leading to a poor visual outcome within the first three decades of life. These patients are commonly diagnosed at an early age and can experience attacks of irritation and photophobia. Further testing will reveal a slightly thinner than average stroma.

Therapeutic options are limited to tinted contact lenses and lubrication, which help reduce symptoms only to a certain extent. The sole treatment is penetrating keratoplasty (PKP), which is a full-thickness corneal transplant that replaces the damaged tissue. Lamellar keratoplasty is typically not indicated due to its high rate of disease recurrence because it involves removing only the anterior cornea and may leave a damaged endothelium attached to the graft.[4]

Granular corneal dystrophy. This condition is characterized by bilateral amorphous hyaline deposits that present within the first decade of life. It is an autosomal dominant dystrophy that has a mutation in the TGFβI gene.[4] Symptoms include glare and photophobia, with decreased vision as it progresses. Patients normally do not experience vision loss until later in life. The cornea will show small breadcrumb-like hyaline deposits in the central superficial stroma that spare the limbus. In the later phase, these deposits increase in number, enlarge and extend deeper into the stroma. RCEs may also occur. Treatment options include PKP or deep anterior lamellar keratoplasty.

Lattice corneal dystrophy. Caused by a mutation in TGFβI gene, this dystrophy manifests as amyloid deposits located in the anterior stroma.[2] The deposits appear as refractile lines centrally in the anterior stroma, while the peripheral cornea remains largely unaffected. Later, these refractile lines progress into stromal opacifications, which can cause patients to be symptomatic with blurred vision. Some patients may lack the typical appearance of



Granular dystrophy type 2 (Avellino dystrophy) showing a central combination of line and circular opacities.

the stromal disease and only experience symptoms from RCEs.[2]

Initially, management is focused on treating any RCEs that occur; but if the opacities become visually significant, PKP may be indicated. Unfortunately, there is a high rate of recurrence of lattice corneal dystrophy within the graft.[4] For surface irregularities, PTK is indicated. Opacities deep within the stroma cannot be treated by PTK because of the depth of involvement. Patients risk corneal haze and overall decreased vision the deeper the ablation depth.

Avellino corneal dystrophy. Also known as granular corneal dystrophy type 2, Avellino is a combination of granular and lattice corneal dystrophies that is caused by a mutation in the TGFβI gene.[2] The affected cornea presents with white-gray granular deposits within the anterior stroma, while the mid-posterior stroma has lattice-like lesions that move more centrally with age. In the late phase, an overall haze can present throughout the cornea.

Management includes copious lubrication, anti-inflammatories or PKP.

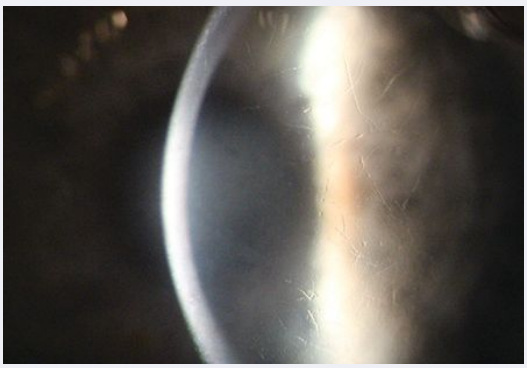
Schnyder corneal dystrophy. This normally presents within the first decade of life, with multiple fine polychromatic crystal deposits that tend to form in a ring shape near the limbus. These deposits are caused by an accumulation of cholesterol and phospholipids that have a strong association with systemic hypercholesterolemia.[7] Patients under the age of 40 with this presentation should have their fasting serum cholesterol and triglyceride levels measured.

Schnyder corneal dystrophy is caused by a mutation in the UBIAD1 gene and is rare.[4] Surgical intervention is seldom needed, as vision is typically unaffected until later in life when the opacities become more central. If vision is significantly affected, a corneal graft may be indicated.[2]

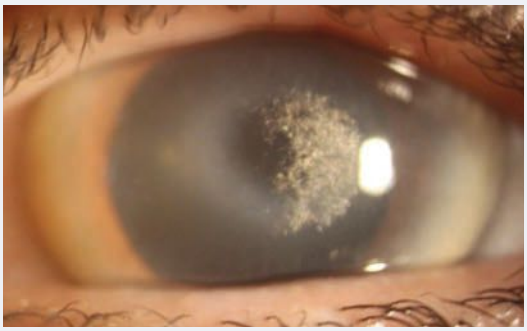
ENDOTHELIAL DYSTROPHIES

The endothelial cell layer represents the most posterior corneal layer. The endothelium is approximately 5µm thick and borders on its basement membrane, Descemet's. This boundary layer's main function is to regulate corneal hydration with active fluid transport to maintain a mostly dehydrated stroma.

Three main corneal dystrophies affect the posterior cornea: Fuchs' endothelial dystrophy (FECD), posterior polymorphous dystrophy (PPCD) and congenital hereditary endothelial dystrophy (CHED). In all three, the endothelial pump function is disrupted, leading to an imbalance of hydration and resultant corneal edema.



Lattice dystrophy on high magnification. Note the progressive corneal haze.



Schnyder corneal dystrophy with an overlying scleral contact lens.

Fuchs' endothelial corneal dystrophy. This is the most common of all the corneal dystrophies in the United States with a prevalence of approximately 4% of the population over age 40.[1] Fuchs' dystrophy is inherited in an autosomal dominant pattern, affecting women more than men.

In FECD patients, the endothelial "pump" cells atrophy, leaving a fewer number of healthy pumping cells and corneal guttata (areas devoid of endothelial cells with thickened Descemet's). Two hallmark endothelial cell morphology changes in FECD are pleomorphism (irregular change to cell shape) and polymegathism (irregular cell growth). As the endothelial cells reduce in number and pump ability continues to worsen, the corneal fluid equilibrium is disrupted and corneal edema ensues. Corneal edema results in loss of visual acuity and visual quality for patients where glare and haloes become a frequently cited visual disruption. In late stage FECD with chronic corneal edema, patients may develop painful bullae (blisters), which over time can alter the anterior corneal shape and epithelial integrity.

Posterior polymorphous corneal dystrophy. This autosomal dominant corneal dystrophy results in abnormal vesicles with deep gray corneal haze at the level of Descemet's and endothelium. The pathophysiology is thought to occur during gestation, and its ocular signs most commonly manifest in early childhood. In the corneal development of patients with PPCD, the endothelial layer is lined with variable amounts of epithelium-like squamous cells.[4] The additional cell layers cause band-like adhesions and

an abnormally thickened Descemet's membrane. The abnormal cell bands can extend from the cornea and adhere to the iris, leading to peripheral anterior synechiae, putting PPCD patients at risk for glaucoma.[4]

Corneal edema typically isn't progressive in patients with PPCD, but if vision in late childhood and early adulthood worsens, clinicians should initiate ancillary tests and a treatment plan to reduce edema.

Congenital hereditary endothelial dystrophy (CHED). The least common of the endothelial dystrophies, CHED has two distinctly recognizable forms: CHED1 and CHED2.[4] A distinguishing factor of both CHED1 and CHED2 is bilateral thickened corneas with a ground glass appearance present at birth or infancy, which is different in onset from other endothelial dystrophies.[4] CHED1 (autosomal dominant) patients manifest progressive corneal edema, tearing and photophobia, but do not have nystagmus.[4] CHED2 (autosomal recessive) tends to be non-progressive, but presents with nystagmus plus occasional deafness (corneal dystrophy-perceptive deafness, a.k.a., Harboyan syndrome).[4]

SURGICAL OPTIONS

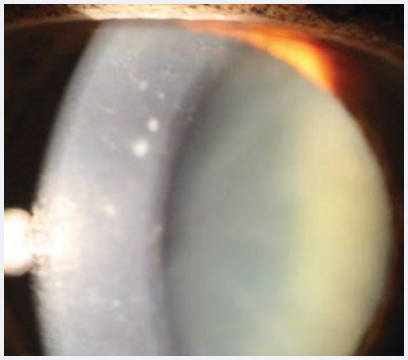
If any of these endothelial dystrophies result in progressive visual loss, relieving stromal edema is the most common treatment approach. Hyperosmotics may provide short-term relief in select patients, but for patients with progressing dystrophies, the best long-term treatment is a surgical approach.

For CHED1 and CHED2, due to stromal ground glass opacification, PKP is the surgical option of choice because corneal edema is less of a concern.[4]

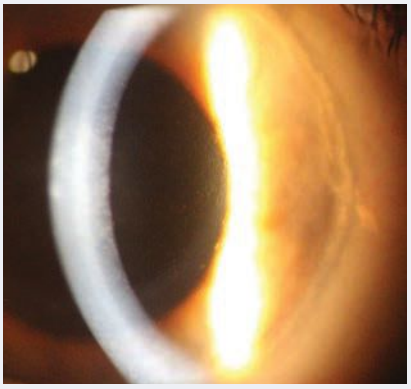
In PPCD and FECD, in which surgical intervention is more dictated by corneal edema, an endothelial keratoplasty is preferred over a PKP. Endothelial keratoplasties are a better option due to less induced astigmatism, avoidance of incremental suture removal, lowered risk of rejection and better visual acuity potential compared with PKP.[8] Descemet's stripping endothelial keratoplasty and Descemet's membrane endothelial keratoplasty (DMEK) are the two most commonly performed endothelial keratoplasties in the United States. Although both provide superior visual acuity results to PKP, DMEK has better visual acuity potential with a quicker visual recovery.[9,10]

Optometry plays a significant role for patients with corneal dystrophies because the initial diagnosis and referral, when necessary, is often made by an OD.

The optometrist's fundamental task for the diagnosis and management of corneal dystrophies is to first determine which corneal layer is affected. Along with the case history, regular corneal topographies and corneal imaging can help to monitor for change and aid in the decision-making for management. Keep in mind that anterior dystrophies most commonly lead to more RCEs and opacification, while posterior dystrophies are associated with more progressive corneal edema. This tenet dictates medical and surgical treatment approaches.



Posterior polymorphous dystrophy in a 17-year-old male.



Fuch's dystrophy with early corneal edema. Note the classic orange peel appearance on the endothelium.

When keratoplasty is necessary, anterior dystrophies require a full-thickness or anterior lamellar transplant; but for patients with posterior dystrophies, an endothelial keratoplasty should be the first choice.

Corneal dystrophies are rare, but correctly diagnosing these conditions changes the eye care landscape for a whole family. RCCL

1. Musch DC, Niziol LM, Stein JD, Kamyar RM, Sugar A. Prevalence of corneal dystrophies in the United States: estimates from claims data. Invest Ophthalmol Vis Sci. 2011 Sep 1;52(9):6959-63.

2. Krachmer J, Mannis M, Holland E (eds.). Cornea. 2nd ed, Vol 1. Philadelphia, PA: Elsevier; 2005: 898-902.

3. Jager RD, Lamkin JC. The Massachusetts Eye and Ear Infirmary Review Manual for Ophthalmology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

4. Klintworth GK. Corneal dystrophies. Orphanet J Rare Dis. 2009 Feb 23;4:7.

5. Dursun D, Kim MC, Solomon A, Pflugfelder SC. Treatment of recalcitrant recurrent corneal erosions with inhibitors of matrix metalloproteinase-9, doxycycline and corticosteroids. Am J Ophthalmol. 2001 Jul;132(1):8-13.

6. Paparo LG, Rapuano CJ, Raber IM, et al. Phototherapeutic keratectomy for Schnyder's crystalline corneal dystrophy. Cornea. 2000 May;19(3):343-7.

7. Bagheri N, Wajda B (eds.). The Wills Eye Manual. 7th ed. Philadelphia: Wolters Kluwer; 2017.

8. Lee WB, Jacobs DS, Musch DC, et al. Descemet's stripping endothelial keratoplasty: safety and outcomes: a report by the American Academy of Ophthalmology. Ophthalmology. 2009 Sep;116(9):1818-30.

9. Tourtas T, Laaser K, Bachmann BO, et al. Descemet membrane endothelial keratoplasty versus Descemet stripping automated endothelial keratoplasty. Am J Ophthalmol. 2012 Jun;153(6):1082-90.

10. Hamzaoglu EC, Straiko MD, Mayko ZM, et al. The first 100 eyes of standardized Descemet stripping automated endothelial keratoplasty versus standardized Descemet membrane endothelial keratoplasty. Ophthalmology. 2015 Nov;122(11):2193-9.

CE TEST ~ NOVEMBER/DECEMBER 2019

1. **All of the following are caused by a mutation in the TGFβI gene, *except*:**
   a. Epithelial basement membrane dystrophy.
   b. Schnyder corneal dystrophy.
   c. Granular dystrophy.
   d. Lattice dystrophy.

2. **What percentage of patients with epithelial basement membrane dystrophy experience recurrent corneal erosions?**
   a. 10%.
   b. 30%.
   c. 50%.
   d. 70%.

3. **Phototherapeutic keratectomy may be indicated for which of the following dystrophies?**
   a. Fuchs' endothelial dystrophy.
   b. Congenital hereditary endothelial dystrophy.
   c. Macular dystrophy.
   d. Epithelial basement membranedystrophy.

4. **Which of the following is an autosomal recessive inherited dystrophy?**
   a. CHED1.
   b. Macular dystrophy.
   c. Granular dystrophy.
   d. Epithelial basement membrane dystrophy.

5. **Which corneal dystrophy is characterized by amyloid deposits within the anterior stroma?**
   a. Granular dystrophy.
   b. Meesmann dystrophy.
   c. Reis-Bucklers dystrophy.
   d. Lattice dystrophy.

6. **Which of the following dystrophies is associated with hypercholesteremia?**
   a. Fuchs' endothelial dystrophy.
   b. Macular dystrophy.
   c. Epithelial basement membrane dystrophy.
   d. Schnyder dystrophy.

7. **What is the correct definition of pleomorphism?**
   a. Irregular change to cell shape.
   b. Irregular cell growth.
   c. Decreased number of cells.
   d. Overproduction of cells.

8. **Which of the following dystrophies is associated with an increased risk for glaucoma?**
   a. Fuchs' endothelial dystrophy.
   b. Posterior polymorphous dystrophy.
   c. Lattice dystrophy.
   d. Granular dystrophy.

9. **Which of the following dystrophies is associated with nystagmus?**
   a. CHED2.
   b. Posterior polymorphous dystrophy.
   c. Macular dystrophy.
   d. Avellino

10. **Descemet's membrane endothelial keratoplasty is indicated for which of the following dystrophies?**
    a. Lattice dystrophy.
    b. Avellino dystrophy.
    c. Epithelial basement membrane dystrophy.
    d. Fuchs' endothelial dystrophy.

EXAMINATION ANSWER SHEET

Unlocking the Mystery of Corneal Dystrophies

Valid for credit through November 15, 2022

Online: This exam can also be taken online at www.reviewsce.com. Upon passing the exam, you can view your results immediately and download a real-time CE ceriticate. You can also view your test history at any time from the website.

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

Mail to: Jobson Healthcare Information, LLC, Attn.: CE Processing, 395 Hudson Street, 3rd Floor New York, New York 10014

Payment: Remit $20 with this exam. Make check payable to: Jobson Healthcare Information, LLC.

Credit: This lesson is approved for 1 hour of CE credit. Course ID is 65002-AS.

Jointly provided by Postgraduate Institute for Medicine and Review Education Group.

Salus University has sponsored the review and approval of this activity.

Processing: There is a four-week processing time for this exam.

Answers to CE exam:

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

Rate the quality of the material provided:

1=Strongly disagree
2=Somewhat disagree
3=Neutral
4=Somewhat Agree
5=Strongly agree

22. The content was evidence-based.
① ② ③ ④ ⑤

23. The content was balanced and free of bias.
① ② ③ ④ ⑤

24. The presentation was clear and effective.
① ② ③ ④ ⑤

Post-activity evaluation questions:

Rate how well the activity supported your achievement of these learning objectives:

1=Poor, 2=Fair, 3=Neutral, 4=Good, 5=Excellent

11. Identify the most common traits as well as the characteristic signs and symptoms related to corneal dystrophies. ① ② ③ ④ ⑤
12. Consider the differential diagnosis for corneal dystrophies. ① ② ③ ④ ⑤
13. Perform the necessary elements of the patient history, ocular examination/vision testing and laboratory testing required to diagnose corneal dystrophies. ① ② ③ ④ ⑤
14. Distinguish the different types of corneal dystrophies most commonly encountered by optometrists, with at least a cursory understanding of their genetic inheritance. ① ② ③ ④ ⑤
15. Provide, or otherwise obtain, the ocular and systemic treatment that the patient requires. ① ② ③ ④ ⑤
16. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one of the following options)
Ⓐ I do plan to implement changes in my practice based on the information presented.
Ⓑ My current practice has been reinforced by the information presented.
Ⓒ I need more information before I will change my practice.
17. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit? (please use a number) _____
18. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)
Ⓐ Apply latest guidelines Ⓑ Change in pharmaceutical therapy Ⓒ Choice of treatment/management approach
Ⓓ Change in current practice referral Ⓔ Change in non-pharmaceutical therapy Ⓕ Change in differential diagnostics
Ⓖ Change in diagnostic testing Ⓗ Other, please specify: _____
19. How confident are you that you will be able to make your intended changes?
Ⓐ very confident Ⓑ somewhat confident
Ⓒ unsure Ⓓ not confident
20. Which of the following do you anticipate will be the primary barrier to implementing these changes?
Ⓐ Formulary restrictions
Ⓑ Time constraints
Ⓒ System constraints
Ⓓ Insurance/financial issues
Ⓔ Lack of interprofessional team support
Ⓕ Treatment related adverse events
Ⓖ Patient adherence/compliance
Ⓗ Other, please specify: _____
21. Additional comments on this course: _____

Identifying information (please print clearly):

First Name _____
Last Name _____
Email _____
The following is your: ☐ Home Address ☐ Business Address
Business Name _____
Address _____
City _____ State _____
ZIP _____
Telephone # ___ - ___ - ____
Fax # ___ - ___ - ____

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

Signature: _____ Date: _____

Please retain a copy for your records. LESSON 118824, RO-RCCL-1119

AT THE Intersection of Sex AND Dry Eye

Biological differences affect a patient's risk of dry eye, pathophysiology and treatment response.

By Cecelia Koetting, OD

While sex differences may not matter for many things in eye care, they can have a significant impact on dry eye disease (DED), according to the Tear Film and Ocular Surface Society's (TFOS) Dry Eye Workshop II (DEWS II) report.[1] In addition to sex, hormones and gender have also been identified as factors that can affect DED diagnosis and treatment.

In the absence of a decent comprehensive report discussing the biological sex differences at a cellular and molecular level, TFOS commissioned one by the Institute of Medicine to help develop a better understanding.[2] The report documents several biological differences between the sexes that manifest themselves in the anatomy, physiology and pathophysiology of the lacrimal gland, cornea, conjunctiva, meibomian glands, nasolacrimal duct and tear film.

In addition, men and women experience pain differently, which impacts the number of patients seeking care for DED and experiencing symptom improvement. Studies show that men have a higher pain tolerance than women, with explanations ranging from sociocultural gender roles to brain neurochemistry differences.[3,4] Thus, male patients are less likely to complain of DED symptoms and are less likely to seek treatment or be compliant with treatment. When they do, they tend to have a greater decrease in symptoms following LipiFlow (TearScience) treatment.[1] Alternately, females may present with symptom complaints that may not match their ocular signs.

Here's how sex, gender and hormones affect a patient's risk for, and diagnosis of, dry eye.

RISKY BEHAVIOR

Overall, the female sex has a higher risk of DED, and women are diagnosed an average of six years younger than their male counterparts.[1,5-8]

Additionally, certain gender-related behaviors and habits can lead to a higher risk of DED, such as the use of cosmetics and contact lens wear, which is higher in women than men. Women are also more likely to undergo LASIK refractive surgery, which carries an elevated risk of post-op DED and neuropathic pain. Animal studies show females have a higher prevalence of neuropathic pain related to DED.[1] Gender- and sex-specific medications, such as hormone replacement therapy and oral contraceptives, can also increase the risk of DED.

SIGNS & SYMPTOMS SEE-SAW

The female sex reports more severe symptoms as measured by the Ocular Surface Disease Index and the Symptom Assessment Questionnaire in Dry Eye. Increased visual quality indicators and feelings of depression accompany this increase in symptoms.[1] The increase in reporting and scoring of symptoms by females may, in part, be why they are diagnosed an average of six years younger than male patients.[1]

Tear osmolarity testing has become common in many optometric offices and can aid in diagnosing and managing DED. The DEWS

Work with the Right Definitions

The most important first step is understanding the difference between sex and gender. The DEWS II report uses the term *sex* to classify organisms, generally as male or female, according to reproductive organs and functions assigned by chromosomal complement. *Gender* is a person's self-representation as male or female, which is often rooted in biology but also shaped by environment and experience.[1]

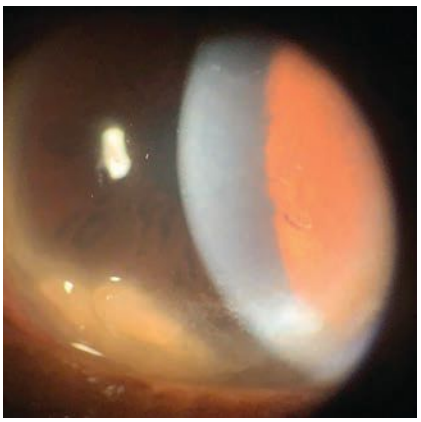
ABOUT THE AUTHOR

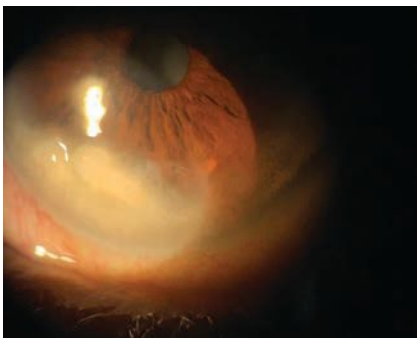
Dr. Koetting is the referral optometric care and externship program coordinator at Virginia Eye Consultants in Norfolk, VA. She is a fellow of the AAO and a trustee of the Virginia Optometric Association.

II report noted that both males and females experience increased tear osmolarity during aging.[1] Incorporating tear osmolarity testing in all older patients may lead to increased and earlier diagnosis of DED patients who may otherwise not have been identified.

Neutral lipids are unstable when spread over an aqueous subphase and will collapse, forming lipid droplets that leave the aqueous portion of the tear film unprotected, allowing for rapid evaporation.[9,10] This layer is stabilized by the lower polar lipid sublayer, so too few polar or too many neutral lipids can cause a tear film imbalance.[9,10] DEWS II researchers note that meibomian gland expression of specific polar lipids in meibum was lower in both middle aged males and females.[1] Specific neutral lipid expression in meibum was higher in older males and females.[1] Both of these results correlate with the finding that the lipid layer is thicker and less contaminated in males older than age 45.[1] It also explains, in part, why in males in the third decade of life experience their highest rate of decreased tear break-up time and females in their seventh.[1]

Within the last few years, more clinicians have started to use meibography to assess patient's meibomian gland function and structure. The TFOS researchers behind DEWS II found that although males have a higher prevalence of asymptomatic meibomian gland dysfuction (MGD), they have greater lid margin abnormality and gland drop out after age 70.[1] This may explain why males have greater decrease in symptoms following LipiFlow treatment.[1]





This postmenopausal female patient has chronic dry eye and bilateral Salzmann's nodules.

Goblet cells found within the conjunctiva are important because they produce and secrete mucins, which in turn hydrate and lubricate the surface of the eye, helping to control chronic inflmmation.[11] Mucin regulation is targeted by allergy and inflammatory mediators that alter the function and survival of the goblet cells.[11] Allergic conjunctivitis leads to an increase in mucin production, while the opposite occurs with DED.[11] With chronic inflammation, inflammatory cytokines cause decreased goblet cell survival, leading to decreased mucin production.[11]

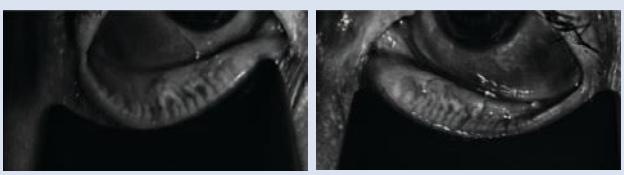
The DEWS II report notes that males have higher goblet cell count, suggesting males may fare better overall when it comes to goblet cell density loss even when compromised by chronic inflammation. Males' higher goblet cell count is also likely related to their higher prevalence of conjunctival inflammation related to allergies.[1]

DEWS II also found women experience a depression of goblet cell count around the time of ovulation.[1] Knowing that females who are ovulating will have cyclically worse dry eye, it may be helpful to individualize their DED treatment and increase their use of medication around their mensturation cycle.

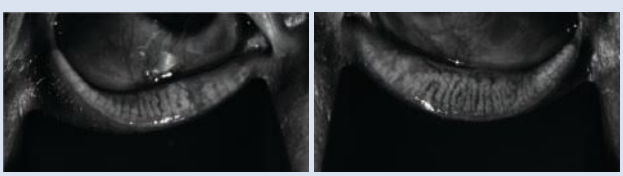
Goblet cell density and production is also affected by other inflammatory processes such as superior limbic keratoconjunctivitis, which is more prevalent in women.[1]

Pterygia, which originate in the conjunctiva and extend onto the cornea, exhibit areas of goblet cell hyperplasia and can occur from many things, such as ultraviolet radiation, inflammatory disorders and chronic ocular surface irritatiton.[12] The DEWS II report finds that pterygia occur more often in males but cause greater discomfort in females.[1] It is important to keep this in mind when

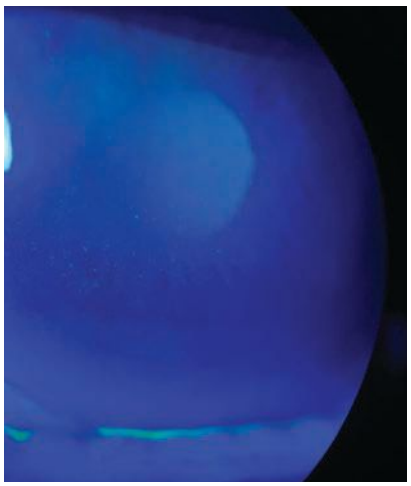
MEIBOGRAPHY COMPARISON BY SEX



Right and left meibography of a 75-year-old female patient with no diagnosed systemic comorbidities.



Right and left meibography of a 75-year-old male patient with no diagnosed systemic comorbidities. Note the male patient of the same age has less gland damage, truncation and atrophy.



This female patient reported severe symptoms, despite signs of only 1+ superficial punctate keratitis.

treating pterygia and making surgical decisions. Even if male patients may be asymptomatic, don't forego the discussion of the risks of progression and don't delay treatment of underlying causes.

Comorbidities, although widely reported in multiple studies to increase the risk of DED, have not been directly studied when it comes to sex-related differences. Research shows lupus, Sjögren's syndrome, rosacea, anxiety, hay fever, depression, pelvic pain, irritable bowel syndrome and chronic pain syndrome are all associated with DED.[1,5] Clinically, most agree with this and have noted increased DED incidence in patients who suffer from these comorbidities. Worth noting is that an all-male study also found an increased rate of DED in those exhibiting high blood pressure and benign prostatic hyperplasia.[6] These conditions are not typically linked with DED, and we may be overlooking these patients.

Both sexes have an increased risk of DED with the use of antidepressants, although women are more likely to use them. Not surprisingly, women who are postmenopausal and on hormone therapy had a 70% increased incidence of DED when on estrogen alone and a 30% increased incidence when on estrogen in combination with progesterone/progestins.[5]

GET TO KNOW HORMONES

Our endocrine system helps us develop and regulate the ocular surface and adnexa. Hormones play an important role in this system, including androgen, estrogen, progestin, estrogen, glucocorticoids, growth hormone IGF-1, insulin and thyroid hormones.

Androgen. This hormone helps in the development and function of the lacrimal glands, meibomian glands, cornea and conjunctiva. The lacrimal gland is an androgen target organ that uses the hormone to help with cellular architecture, gene expression, protein synthesis, immune activity and fluid and protein secretion.[1]

Shortage can cause lacrimal gland dysfunction and aqueous tear deficiency. Women have a decrease in serum androgen and increased primary lacrimal gland deficiency during menopause, pregnancy, lactation and with use of estrogen containing oral contraceptives.

Sjögren's patients, more commonly women than men, have a greater androgen deficiency within their lacrimal tissues related to the elevated pro-inflammatory cytokines IL-1, TNF-α and IL-6.[1] This androgen deficiency impairs lacrimal gland function, which is a risk factor for lacrimal gland inflammation and aqueous-deficient DED.[1]

The meibomian gland complex is also an androgen target organ, stimulating tissue function and suppressing keratinization.[1] Androgen stimulates the ontologies responsible for lipid biosynthesis and cholesterol, fatty acid, phospholipid and steroid dynamics.[1] Androgen deficiency is a risk factor for the development of MGD and evaporative DED.

Androgen is also important for corneal and conjunctival cell reproduction and synthesis. Deficiency can lead to poor wound healing, corneal dystrophies and increased conjunctival and corneal staining.[1] Studies exploring topical and systemic applications show an improvement in DED signs and symptoms in both men and women.[1]

Estrogen and progesterone. Unlike androgen, less is understood about the roles of estrogen or progesterone in ocular surface function. No intra-tissue data currently exists; however, both hormones have been detected in human tears, correlating with serum levels in premenopausal females.[1] Estrogen receptors are found in the meibomian glands, lacrimal gland, cornea, bulbar conjunctival and tarsal plate.[1]

Estrogen plays an important role within our immune system, the extent of which differs significantly based on concentration and tissue type. This hormone promotes the production of B-cells and antibodies, a subset of T-cells, dendritic cells, M2 macrophages and regulatory cytokines.[1]

Reports on the effect of estrogen and progesterone on DED are varied depending on the study and co-factors such as autoimmune conditions.[1] Although studies show positive effects of topical testosterone on MGD and DED, it is currently only available via compounding pharmacies.[9] Allergan submitted a patent and initiated a Phase II study in 2015, but nothing has been published at this time. Similarly, compounded estradiol suspension or a mixture containing testosterone and progesterone are used by some practitioners to treat DED off label.

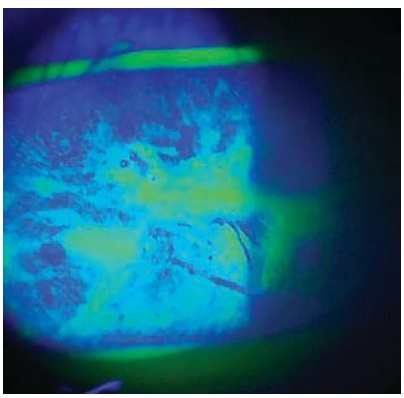
Glucocorticoids. Functioning as a regulator of the inflammatory response and immunosuppressive hormone, glucocorticoid and its synthetic partners are important in

anti-inflammatory activity.

Glucocorticoid's effects on the ocular surface and adnexa are concentration dependent and have a higher level of anti-inflammatory activity in males than females.[1] The ocular surface of the mucosa is immunoprotected in part by the autocrine effect in epithelial cell and fibroblasts caused by production of cortisol from endogenous glucocorticoid.[1]

With a better understanding of these hormones' role in DED, researchers have developed and continue to develop new treatments. Topical glucocorticoids are already widely used to control inflammation-associated DED. A phase IV study recently finished, but has not published results, on topical hydrocortisone 0.335% (Softacort, Thea Pharmaceuticals) to treat chronic DED and ocular inflammation. Another ongoing study is looking at the effects of intravenous glucocorticoid on the tear film in eyes with thyroid-associated ophthalmopathy.

With the currently available topical steroids, clinicians should take the preservatives within the drug into consideration, as many with DED are also sensitive to these. Compounding pharmacies are a great alternative for preparation of preservative-free topical corticosteroids. This option also allows for control of the drug's concentration, helping to decrease concern for complications with longer-term use.



This poorly controlled diabetic patient is treated for chronic severe DED and neurotrophic keratoconjunctivitis, which has led to recurrent corneal abrasions.

Growth hormone, IGF-1 and Insulin. The latter of these hormones, secreted by the acinar cells within the lacrimal gland, is found within the human tear film and its receptor, IGF-1, is found on the human ocular surface. Growth hormone and IGF-1 may help within the meibomian glands to regulate growth and function.[1]

Insulin helps with corneal wound healing by promoting tissue maintenance.[1] Diabetic patients have delayed corneal healing in part because their tears exhibit increased IGF-binding protein 3, which may attenuate the IGF-1 receptor signal necessary for tissue maintenance.

Diabetes patients often suffer from DED due to the autoimmune destruction of the lacrimal gland from antigen cross activity with the pancreas in Type 1 diabetes. DED in patients with Type 2 diabetes is both hormonal and metabolic in nature stemming from the defective insulin action and hyperglycemia.

Sex hormones are thought to influence the levels of insulin receptor, suggesting higher levels of sex hormones lower the action of insulin within ocular tissues. Patients with insulin resistant conditions such as polycystic ovary syndrome, pregnancy, anti-androgen therapy and androgen insensitivity syndrome have increased DED symptoms.

Animal studies looking at systemic replacement or topical insulin treatment show that signs of DED and wound healing defects can be reversed. Current use of autologous serum, which contains insulin and growth factors, is an effective treatment for severe DED and conditions associated with it, although it is widely underused due to preparation and storage inconveniences.

Thyroid. An imbalance of thyroid hormones T3 and T4 has a negative effect on the lacrimal gland, tear film and ocular surface.[1] These hormones help to promote lipid and protein synthesis along with tissue growth.[1] Females are more prone to thyroid diseases such as Hashimoto's thyroiditis and Graves' disease. These patients are also more likely to have Sjögren's syndrome.

Our understanding of DED has evolved significantly in the last 10 years, as has our diagnostic technology and treatment options. Understanding the underlying cause and how sex and gender impact the physical, hormonal and behavioral differences are crucial to ensure an appropriate treatment approach. RCCL

1. Sullivan D, Rocha E, Aragona P, et al. TFOS DEWS II sex, gender, and hormones report. Ocul Surf. 2017;15(3):284-333.

2. Institute of Medicine (US) Committee on Understanding the Biology of Sex and Gender Differences: Exploring the Biological Contributions to Human Health: Does Sex Matter? Washington, DC: The National Academies Press; 2001.

3. Mogil, Jeffrey S. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. Nat Rev Neurosci. 2012;13(12):859.

4. Ruau D, Liu LY, Clark JD, et al. Sex differences in reported pain across 11,000 patients captured in electronic medical records. J Pain. 2012;13(3):228-34.

5. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003;136(2):318-26.

6. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Arch Ophthalmol 2009;127:763e8.

7. Paulsen AJ, Cruickshanks KJ, Fischer ME, et al. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol. 2014;157(4):799-806.

8. Muoz B, West SK, Rubin GS, et al. Causes of blindness and visual impairment in a population of older Americans: The Salisbury Eye Evaluation Study. Arch Ophthalmol. 2000;118(6):819-25.

9. Green-Church K, Butovich I, Willcox M, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on tear film lipids and lipid-protein interactions in health and disease. Invest Ophthalmol Vis Sci. 2011;52(4):1979-93.

10. Shrestha R, Borchman D, Foulks G, et al. Analysis of the composition of lipid in human meibum from normal infants, children, adolescents, adults, and adults with meibomian gland dysfunction using 1H-NMR spectroscopy. Invest Ophthalmol Vis Sci. 2011;52(10):7350-8.

11. Dartt DA, Masli S. Conjunctival epithelial and goblet cell function in chronic inflammation and ocular allergic inflammation. Curr Opin Allergy Clin Immunol. 2014;14(5):464-70.

12. Golu T, Mogoantă L, Streba CT, et al. Pterygium: histological and immunohistochemical spects. Rom J Morphol Ebryol. 2011;52(1):153-8.

By Cory Collier, OD

The "Wow" Starts Now

Correcting residual astigmatism can be the difference between a good visual outcome and a great one.

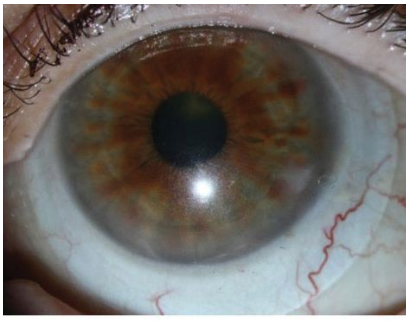
It can be easy to get lost in the customization options available with scleral lenses. While most help create healthy and comfortable lenses, front toric vision correction stands out from the rest. Sometimes, it can be the difference between a satisfied patient and a loyal patient.

THE CASE

A 73-year-old female presented for a second opinion on her contact lens correction. The patient's chief complaint was poor visual quality in her right eye due to glare and ghosting. She was diagnosed with Salzmann's nodular corneal degeneration 15 years earlier and has been wearing corneal gas permeable (GP) lenses for over 40 years. She was refit with a piggyback lens system three years earlier to improve the centration of her lenses. Lately, however, she has been experiencing frustration as a result of her visual symptoms. She was interested in any contact lens option that would improve visual quality.

Slit-lamp examination revealed superior nasal, elevated gray-blue nodules consistent with her corneal degeneration diagnosis. The ocular surface was otherwise unremarkable.

The patient's GP lenses were highly decentered inferior temporal in both eyes. The superior nasal nodules appeared to play a role in decentration, as they displaced the lenses inferior and temporal in both eyes. Acuities were measured at 20/40 OU. A +0.50 spherical over-refraction improved vision to 20/30 OU, and a sphero-cylindrical over-refraction improved it to 20/20 OU. It was unclear if lens decentration, flexure or true residual astigmatism was resulting in the toric over-refraction.



The flat meridian "O" is rotated 30 degrees to the left, and the front cylinder vertical reference is at 6 o'clock OS.

Although the patient had potential for improved vision based on the results of the over-refraction, the current piggyback lens design made this unlikely for two reasons. First, decentration would continue to be a major limiting factor as the nodules displaced the lens. Even with piggybacking, the current centration was not adequate. This decentration was likely contributing to the glare symptoms as her pupil approached the limits of her optic zone. In addition, if true residual astigmatism were present, a front toric corneal design would be difficult to stabilize due to the superior corneal nodules displacing the lens inferiorly. It also has unpredictable rotational stability, as the lens edge contacts the corneal nodules with each blink.

After reviewing possible approaches, a scleral lens was the best option. This would provide the opportunity for GP optics, centration independent of corneal anatomy, a larger optic zone to limit interaction with mydriasis in low lighting and the opportunity to incorporate a stable front toric correction if needed.

DIAGNOSTIC FITTING

The diagnostic lens chosen for both the right and left eyes was the Custom Stable Elite (Valley Contax) -2.00D/45.00D/16.8mm with standard limbal and scleral zones [+6 (flat)/-4 (steep)].

Following 30 minutes of settling, central clearance OD was 250µm with approximately 75µm of clearance over the most elevated corneal nodule located in the mid-peripheral cornea, and the limbal clearance was roughly 25µm in all quadrants. The scleral zone displayed mild edge lift along the flat meridian (this design uses two laser-marked "Os" to indicate the flat meridian) with alignment along the steep meridian.

The flat meridian was rotated 25 degrees to the right using the horizontal meridian as a reference. The left eye displayed 200µm centrally with 50µm of clearance over the most elevated corneal nodule located in the superior-nasal peripheral cornea. The limbal clearance was full at roughly 25µm in all quadrants. The scleral zone displayed moderate edge lift along the flat meridian with alignment along the steep meridian. The flat meridian was rotated 30 degrees to the left. Both lenses were well centered.

A spherical over-refraction of +1.50 OD and +1.25 OS improved vision to 20/30+ OD and OS and 20/30+2 OU. A sphero-cylindrical over-refraction yielded +1.75-0.75x050 OD and +1.50-0.75x130 OS. This resulted in acuities of 20/20 OU. Over-keratometry was performed with a spherical result, ruling out lens flexure as the potential cause of the cylindrical over-refraction.

Based on these results, the following lenses were ordered: -0.25-0.75x025 (25-degree right

rotation)/45.00D/16.8mm/limbal clearance zone: standard/scleral landing zone: +4 (flat)/-2 (steep) OD and -0.50-0.75x160 (30-degree left rotation)/45.00D/16.8mm/limbal clearance zone: standard/scleral landing zone: +2 (flat)/-2 (steep) OS.

Both lenses were modified in the flat meridian of the scleral zone to compensate for edge lift, while the steep meridians were left standard. The over-refraction axis was adjusted to compensate for lens rotation.

DISPENSING

The patient returned one week later. As is typical in our office, the patient's lenses were inserted, and she was given approximately 30 minutes for them to settle.

Upon entering the exam room, the patient said, "I have one word for you—'Wow!'" She went on to comment that she couldn't recall the last time her vision felt so crisp and clear. Her acuities were 20/20 OU with a plano over-refraction in both eyes. The central fit of both lenses was consistent with the diagnostic fit. The flat meridian markings were rotated to the same degree as they were in the diagnostic fitting. Within this lens design, an additional vertical laser mark was placed at the anticipated 6 o'clock position for a simple axis check. The patient was educated on all pertinent wear and care instructions.

FOLLOW-UP

The patient returned a week later having worn her lenses for seven hours. She praised her visual quality, reporting excellent initial and lasting comfort and vision with a daily average wear time of 12 hours. In addition, she had noticed a reduction in glare while driving at night. Her acuities were 20/20 OU, and her central clearances were 200µm and 150µm in the right and left eyes, respectively. Roughly 25µm of clearance over the most elevated nodules, full limbal clearance and scleral alignment was observed in both eyes. Rotation was consistent with previous measures.

The patient returned for her one-month follow-up with continued clarity and comfort. The fit was unchanged, and her ocular surface tolerated lens wear well.

DISCUSSION

Scleral lenses offer excellent stability on the eye. With this stability comes the ability to incorporate front toric vision correction with predictable rotational stability.

Front toric scleral lenses can be stabilized through prism ballasting and toric scleral shape. When a front toric correction is added to a lens with a symmetrical scleral zone design, the lens must be balanced using prism ballasting to minimize lens rotation. The amount of recommended ballasting varies based on lens design. The ballast can be increased if unstable rotation is observed; however, keep gravity and oxygen availability in mind.

With the ballast adding weight to the inferior portion of the lens, inferior decentration can be problematic when excess amounts of prism are incorporated. In addition, the thickness of the inferior lens can present challenges with oxygen availability to the inferior cornea. Use the least amount of ballast to stabilize the lens and high- to hyper-Dk materials.

A more favorable situation arises when scleral toricity can be used to stabilize the lens. When toric scleral zones are appropriate, the interaction between the toricity in the shape of the lens and the toricity of the sclera creates rotational stability. This allows for stability without the added weight or thickness. A diagnostic set with standard toricity is extremely helpful in determining the lens power to order. By carefully measuring the rotation of the diagnostic lens, the over-refraction axis can be properly compensated.

Considering the right eye of the patient in this case, the diagnostic lens was rotated 25 degrees to the right; thus, the axis of the over-refraction was modified from 50 degrees to 25 degrees. Note that this compensation is performed on the over-refraction, not the manifest refraction. We anticipate the ordered lens will rotate the same amount of degrees as the diagnostic lens. If this is the case, the axis will align as intended. Some scleral lens designs provide additional rotation assessment lens markings to ensure that the predicted rotation with the diagnostic lens is the observed rotation with the ordered lens.

During the diagnostic fitting process, I always perform both spherical and sphero-cylindrical over-refractions to gauge the patient's best-corrected acuity and identify meaningful amounts of residual astigmatism (I consider a front toric when residual astigmatism is 0.75 or greater). By addressing meaningful residual astigmatism, we are able to aid our patients in achieving their full visual potential and improving their overall quality of vision and satisfaction with their lenses. RCCL

By Mile Brujic, OD, and David Kading, OD

The ABCs of EBMD

Although the presentation of epithelial basement membrane dystrophy may be subtle, its visual outcomes may not be.

Epithelial basement membrane dystrophy (EBMD) may be more common than we think. Literature suggests that it affects 2% to 3% of the global population.[1,2] This is probably an underestimate, as EBMD is sometimes overlooked because of how subtle its clinical appearance can be. Here's how to spot and manage it.

CLINICAL PRESENTATION

EBMD happens when the basement membrane (BM) extends into the corneal epithelium. Basal corneal epithelial cells produce abnormal BM cells, leading to the region's irregularity.[2-4] As this occurs, the epithelium becomes uneven over the irregularly heaped areas of membrane, creating the elevations clinically seen as areas of negative staining and patterns of mapping, dots and fingerprints. Elevated epithelium due to BM irregularities is thinner than corresponding non-elevated epithelial tissue. This can be easily seen with AS-OCT (*Figure 1*).

As EBMD progresses, it can cause a progressive reduction in BCVA. Unfortunately, often this leads to variability in vision because of poor tear film qualities over the corneal irregularities and variability in the irregular patterns observed on the cornea. These patients' refractive errors can vary with manifest refractions over separate visits. Usually this is seen as changes in the axis and amount of astigmatism measured.

VISION OPTIMIZATION

EBMD management strategies focus on promoting the health of the tear film and ocular surface. If any abnormalities exist, it is critical to treat them appropriately. In the presence of a normal tear film and ocular surface, lubrication via artificial tears, punctal plugs, Lacriserts or a combination of the three may be used.

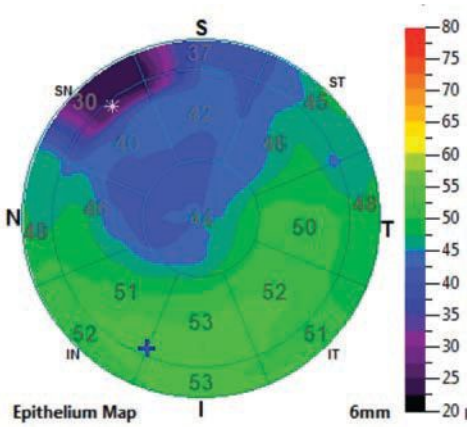


Fig. 1. Epithelial thickness map shows thinning where the map pattern is located.

A major concern for patients with EBMD is recurrent corneal erosion. Preventative measures include lubrication in the evening with bland and hyperosmotic saline ointments. More aggressive strategies to reduce the risk of recurrent events include epithelial debridement and phototherapeutic keratectomy.[5-7]

In the event of a recurrent erosion, the goal is to rehabilitate the cornea. In mild cases, a bandage contact lens can help the cornea heal. If the erosive event is more severe, consider an amniotic membrane.[8]

For patients who have a difficult time seeing well and experience fluctuating vision, there are several contact lens options that can improve the visual experience by renormalizing surface irregularities to create a smooth, regular optic surface.

EBMD patients can minimize their need for glasses with the appropriate lens prescription. In mild cases, a soft contact lens can accomplish this. Although no clear guidelines exist for soft lens selection, higher modulus lenses, such as silicone hydrogel options, work well for these patients. With ever-advancing technologies, we now have a handful of daily disposable lens options that are silicone hydrogel. For more moderate or severe corneal irregularities secondary to EBMD, oftentimes a rigid surface is required to renormalize the optics entering the eye. Small-diameter gas permeable lenses work well for EBMD patients. If a patient has a difficult time wearing this lens, a hybrid may be an appropriate alternative. Scleral lenses are also an option and correct corneal irregularities through the post-lens solution reservoir and lens surface.

CASE STUDY

A 45-year-old male presented with a chief complaint of blurred vision. He noted that everything "seemed blurry" and driving at night was becoming much more difficult for him. He reported that his glasses were re-made three times but the prescription was never correct. His manifest refraction was different than what was in his glasses. His VA was 20/25 OU.

The posterior segment examination was unremarkable. The patient's corneas were remarkable for significant mapping patterns that were visible when viewed with a cobalt blue light and a written #12 filter after fluorescein was placed on the

surface of the eyes (*Figure 2*). EBMD patients have elevated regions on the corneal surface that appear darker or black when compared with the surrounding cornea because they are not adequately covered by the tear film (*Figure 3*).

The patient was educated on the reason for his reduced and variable vision. We discussed treatment options, and he wanted to proceed with lenses to improve his vision. He was fit with scleral lenses of the following parameters: -2.00/16.5mm diameter/4200 sagittal depth/toric scleral landing zone OU.

After the lenses were worn for 30 minutes, the central corneal clearances measured with a horizontal scan were 220µm OD and 240µm OS. There was adequate limbal clearance, and the landing zone was slightly flat in the steep meridian. The steep meridian was oriented vertically on the eye with a marking indicating it was located at the 6 o'clock position. The over-refraction was -0.50 SPH 20/15 OD and -0.25 SPH 20/15 OS.

With the diagnostic lenses, the patient reported that his vision was better than it had been in years. He commented on how sharp everything looked. We ordered lenses with the appropriate powers and Hydra-PEG (Tangible Science) coating to optimize the hydrophilic properties of the lens surface and steepened the landing zone in the steep meridian by two steps.

With the lenses, the patient's VA was 20/20 OU. In addition to improved vision and visual quality, the patient commented on how comfortable the lenses felt. He was taught appropriate wear and care practices before the lenses were dispensed.

The patient noted good comfort and vision at his one-week follow-up. His vision was 20/15 OU with no notable over-refraction. He continues to find success with scleral lens wear and experience clearer vision.

A specialty contact lens improved the quality of this patient's vision and could be the solution for others like him. Practicing appropriate treatment methods, including advanced contact lens fittings and surgical remedies, presents an important opportunity to intervene in an EBMD patient's life and help optimize their vision for the best outcomes. You just need to know where to start and how to proceed. RCCL

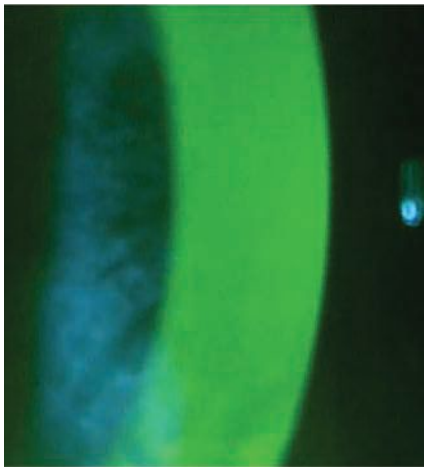


Fig. 2. Normal fluorescein pattern over the cornea.

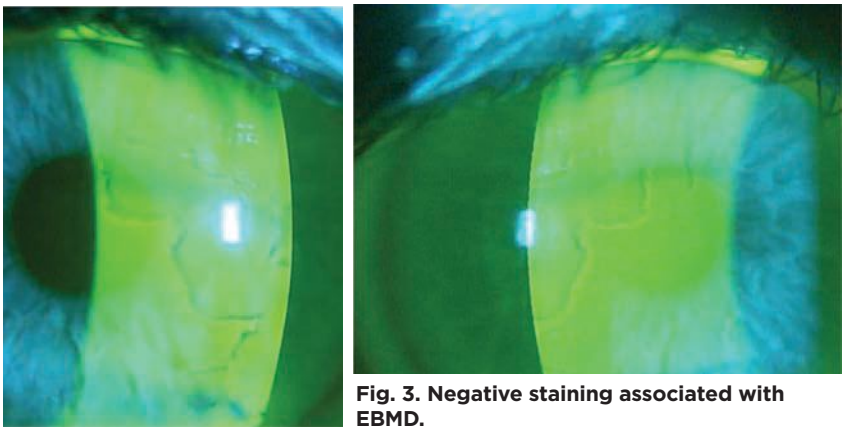


Fig. 3. Negative staining associated with EBMD.

1. Hillenaar T, van Cleynenbreugel H, Remeijer L. How normal is the transparent cornea? Effects of aging on corneal morphology. Ophthalmology. 2012;119(2):241-8.

2. Waring GO 3rd, Rodrigues MM, Laibson PR. Corneal dystrophies. I. Dystrophies of the epithelium, Bowman's layer and stroma. Surv Ophthalmol. 1978;23(2):71-122.

3. Labbé A, Nicola RD, Dupas B, et al. Epithelial basement membrane dystrophy: evaluation with the HRT II Rostock Cornea Module. Ophthalmology. 2006;113(8):1301-8.

4. Karpecki PM, Shechtman DL. Put an end to EBMD. Rev Optom. 2008;145(3).

5. Reidy JJ, Paulus MP, Gona S. Recurrent erosions of the cornea: epidemiology and treatment. Cornea. 2000;19(6):767-71.

6. Vo RC, Chen JL, Sanchez PJ, et al. Long-term outcomes of epithelial debridement and diamond burr polishing for corneal epithelial irregularity and recurrent corneal erosion. Cornea. 2015;34(10):1259-65.

7. Lee WS, Lam CK, Manche EE. Phototherapeutic keratectomy for epithelial basement membrane dystrophy. Clin Ophthalmol. 2016;11:15-22.

8. Miller DD, Hasan SA, Simmons NL, et al. Recurrent corneal erosion: a comprehensive review. Clin Ophthalmol. 2019;13:325-35.

By Christine W. Sindt, OD

A Knotty Problem

Sutures pose a challenge for contact lens fitting, necessitating an elevation-specific design.

An 18-year-old male with Stevens-Johnson syndrome presented after glaucoma tube explantation secondary to tube exposure and endophthalmitis. The patient was suffering from a persistent corneal epithelial defect and was referred for scleral lens fitting to aid in corneal healing of his only remaining eye.

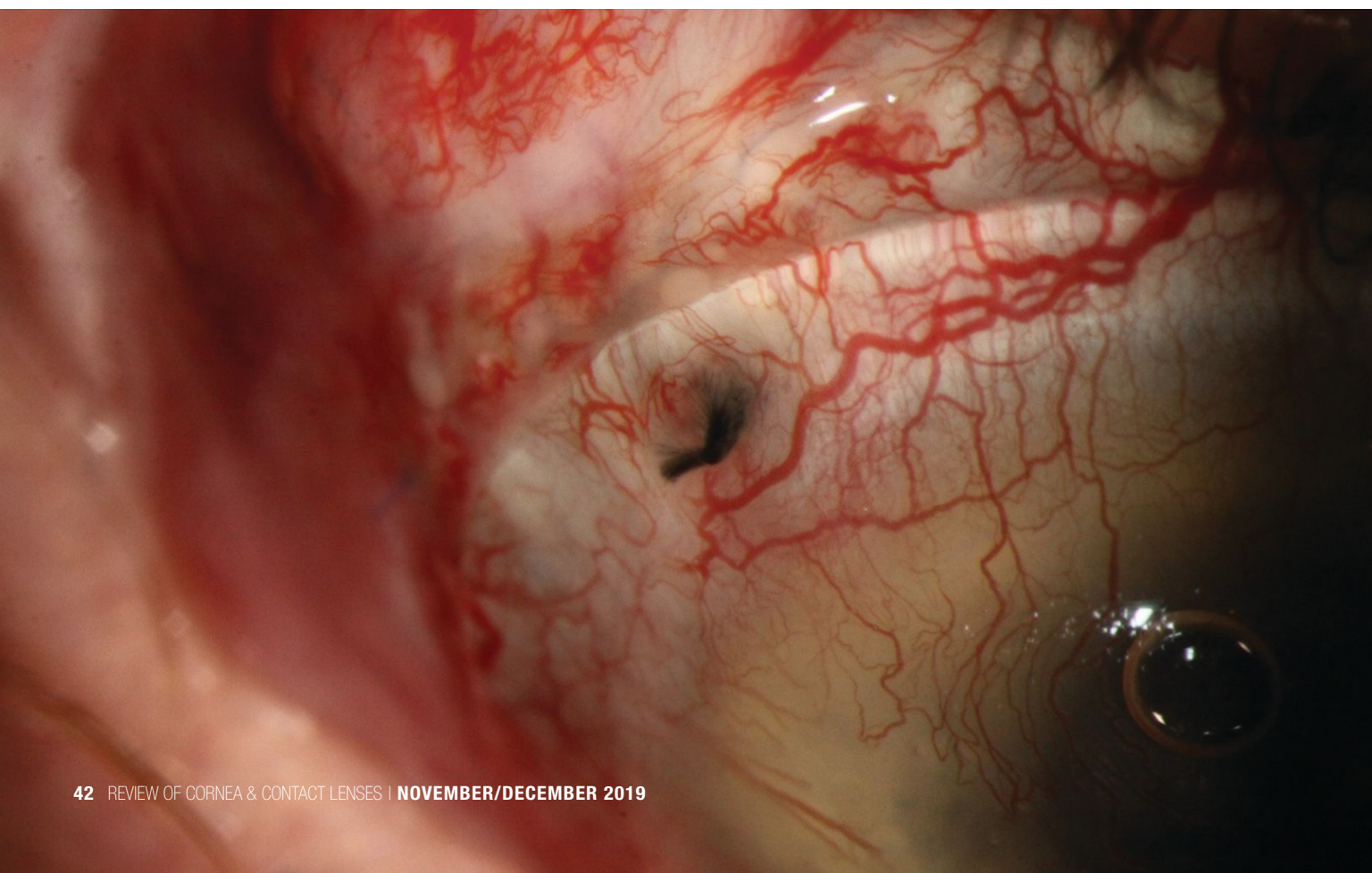
The conjunctival wound had been closed with three running 8-0 vicryl sutures with episcleral bites to anchor to the underlying sclera. There was a suture knot with long tails under the conjunctival flap. An elevation-specific lens was created with extra clearance over the knot and the corneal epithelial defect was closed within days. The patient remained on all postoperative antibiotics, steroids and glaucoma meds during scleral lens wear. At follow up, the suture tails were splayed out under the scleral lens haptic; however, there was no staining or erosion of the conjunctival tissue.

Contact lenses are commonly fit over ocular sutures. When doing so, it is important to follow the patient closely for suture erosion, which may be a vector for infection.

Vicryl (polyglactin 910) is an absorbable suture that holds its tensile strength for approximately 21 days and is completely absorbed within 56 to 70 days. It is used for subcutaneous tissue, muscle reattachment, cornea and conjunctival procedures. It undergoes hydrolytic degradation and has been known to elicit inflammatory reactions. Granulomas may form around vicryl conjunctival/scleral sutures.

It is a braided material, which accounts for the splayed appearance seen in this patient. He will need to be refit with a new elevation-specific lens design once the suture is absorbed and the surgical inflammation is reduced.

Ethilon (nylon) is a non-absorbable monofilament material commonly used for corneal transplants. This material will remain in the cornea until removed. Fortunately, it is inert, with minimal tissue reaction. RCCL



SYSTANE® COMPLETE:

OUR MOST ADVANCED SOLUTION.
ONE SIMPLE CHOICE.

Our most innovative drop supports all layers of the tear film and is designed to provide symptom relief for **every major type of dry eye**:[1-9]

- ☑ **Evaporative Dry Eye**
- ☑ **Aqueous-deficient Dry Eye**
- ☑ **Mixed Dry Eye**

The Relief is Real™

Advanced, lipid nano-droplet technology rapidly delivers the lubricant across the ocular surface — resulting in **better coverage* to provide fast-acting hydration, tear evaporation protection, and long-lasting relief**[1,5-6,8-10]

VISIT SYSTANE.COM TO LEARN MORE!

*Compared to SYSTANE® BALANCE Lubricant Eye Drops.

References: 1. Korb D, Blackie C, Meadows D, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference of the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy. **2.** Moon SW, Hwang JH, Chung SH, Nam KH. The impact of artificial tears containing hydroxypropyl guar on mucous layer. *Cornea*. 2010;29(12):1430-1435. **3.** Davitt WF, Bloomenstein M, Christensen M, Martin AE. Efficacy in patients with dry eye after treatment with a new lubricant eye drop formulation. *J Ocul Pharmacol Ther*. 2010;26(4):347-353. **4.** Willcox MDP, Argueso P, Georgiev GA, et al. TFOS DEWS II tear film report. *Ocul Surf*. 2017;15:366-403. **5.** Ketelson H, Rangarajan R. Pre-clinical evaluation of a novel phospholipid nanoemulsion based lubricant eye drop. Invest Ophthalmol Vis Sci. 2017;58:3929. **6.** Ogundele A, Ketelson H, et al. Preclinical evaluation of a novel hydroxypropyl-guar phospholipid nanoemulsion lubricant eye drop for dry eye disease. Poster presented at: The 36th World Ophthalmology Congress (WOC); June 16-19, 2018; Barcelona, Spain. **7.** Craig J, Nichols K, Akpek E, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15:276-283. **8.** Lane S, Paugh J, et al. An Evaluation of the in vivo Retention Time of a Novel Artificial Tear as Compared to a Placebo Control. Invest Ophthalmol Vis Sci. 2009;50(13):4679. **9.** Benelli U. Systane® lubricant eye drops in the management of ocular dryness. *Clin Ophthalmol*. 2011;5:783-790. **10.** Torkildsen G. The effects of lubricant eye drops on visual function as measured by the Inter-blink interval Visual Acuity Decay test. *Clin Ophthalmol*. 2009;3:501-506.

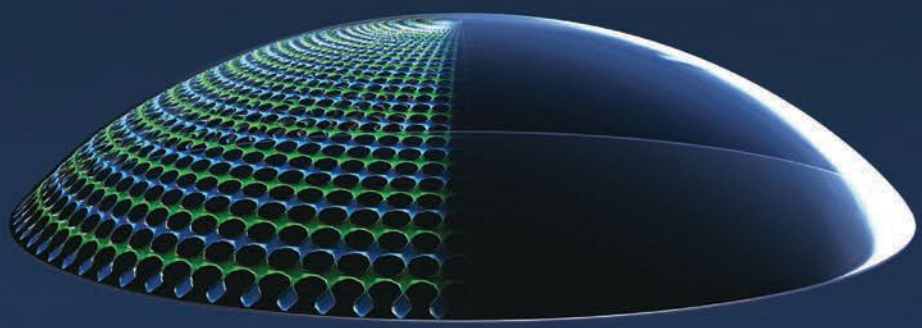
Alcon A Novartis Division

Technology in balance

Health Vision Comfort

Miru 1month: a unique family of silicone hydrogel monthly lenses.

MeniSilk™ and **Nanogloss™** technologies designed to meet the demands of today's contact lens wearer.*



Material and surface technologies

MeniSilk™

- Ultra high Dk/t - 161 @ -3.00D
- Exceptional hydration
- Optimized transparency

Nanogloss™

- Super smooth surface
- Resistance to bacteria
- Excellent wettability

Menicon

www.meniconamerica.com

*Menicon data on file April 2016