RCCL®
REVIEW OF CORNEA & CONTACT LENSES
JANUARY/FEBRUARY 2023

CORNEAL DISEASE Layer

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REVIEW OF CORNEA & CONTACT LENSES

CORNEAL DISEASE

Layer By Layer

NEUROPATHIC PAIN • CLs FOR KERATOCONUS • RECURRENT CORNEAL EROSION • PERIPHERAL ULCERATIVE KERATITIS

We're willing to bet most eye care professionals don't realize just how prevalent *Demodex* blepharitis is.[1]

In fact, ~**25 million eye care** patients in the US may have *Demodex* blepharitis (DB).[2]

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References: 1. Data on file, Tarsus Pharmaceuticals, Inc. June 2022. **2.** O'Dell L et al. *Clin Ophthalmol.* 2022;16:2979-2987.

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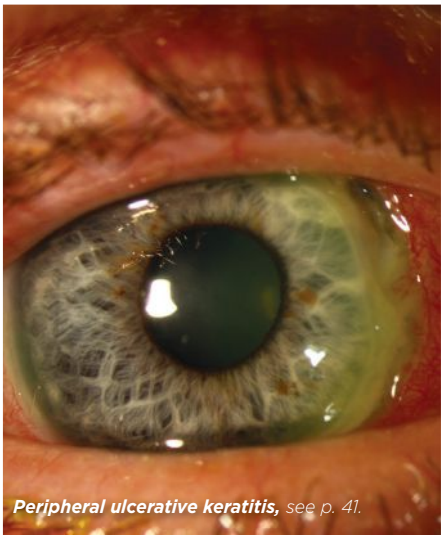
contents

Review of Cornea & Contact Lenses | January/February 2023



Peripheral ulcerative keratitis, *see p. 41.*

departments

features

IN BRIEF

■ **Having an active lifestyle can reduce the risk of a host of health problems, one of which is DED**, suggests evidence from a new study in *Ocular Surface*. The researchers found an association between greater sedentary behavior and increased risk of dry eye. In addition, **less screen use and more physical activity seemed to attenuate the increased risk of DED, even in those living more sedentary lifestyles.**

Participant data (*n*=48,418) was sourced from a population-based cohort study called Lifelines. Of all participants, 9.1% had DED. "Greater sedentary behavior was associated with increased risk of DED (OR: 1.02 per hour/day)," the researchers reported. However, **the association was only significant for those with physical activity levels below what's recommended by the WHO (150 minutes of moderate or 75 minutes of vigorous activity per week).**

The team concluded in their paper that **"screen use, medical comorbidities and sufficient physical activity should be considered key confounding factors in the relationship between sedentary behavior and DED."**

Nguyen L, Magno MS, Utheim TP, et al. The relationship between sedentary behavior and dry eye disease. Ocular Surface. January 5, 2023. [Epub ahead of print].

■ A recent study observed that **corneal staining, TBUT, tear osmolarity and a composite severity score of DED signs were significantly more severe with increasing age in women, but for men, symptoms didn't worsen with increasing age.** When hypothesizing reasons as to why dry eye signs worsen with age, the researchers noted that "**It's possible that changes in epithelial damage and DNA alterations are exacerbated by inflammatory processes in the conjunctival epithelium, corneal epithelium and accessory lacrimal glands, which are more likely to occur with the progression of time in one's lifetime,.**"

As to why dry eye signs worsen in women, the study authors explain that, based on other research, **"there are likely factors other than estrogen receptor expressivity involved with the relationship of DED signs in relation to both sex and increasing age."**

Zhao M, Yu Y, Ying GS, et al. Age associations with dry eye clinical signs and symptoms in the Dry Eye Assessment and Management (DREAM) Study. January 5, 2023. [Epub ahead of print].

Red Light Therapy Reduces Axial Lengthening in Some Kids

The greatest effects were seen in younger children and those with longer baseline lengths.

A key characteristic of myopia, axial lengthening may predispose an individual to future retinal complications such as macular hemorrhage, glaucoma, retinal detachment or cataracts. Treatments aimed at slowing axial lengthening such as low-dose atropine drops and increased time spent outdoors are currently being investigated.

Another promising treatment on the horizon is repeated low-level red light (RLRL) therapy. This novel therapy, available internationally but not yet in the US, was found to not only reduce myopia progression and axial lengthening but also shorten axial length (AL) in some kids. This unexpected finding was first reported in a randomized multicenter study in Chinese children in 2022.[1] Following that, researchers conducted an additional study to assess the effect of RLRL therapy in a clinical setting and find out which factors were associated with AL shortening in certain children.[2] While further studies are needed, the researchers observed greater AL shortening among younger children who had longer baseline axial lengths.

Photo: Eyerising International

Repeated low-level red light therapy, developed by Australian company Eyerising International, is a novel treatment for myopia that's been shown to slow axial lengthening and even reverse it in some children.

This retrospective clinical study included 434 myopic children between the ages of three and 17 (mean age: 9.7) who had undergone RLRL therapy for at least a year using a home-use desktop light device that emitted 650nm wavelengths. Primary outcomes were frequency of AL shortening and associated factors.

The researchers reported that 26.5% of children experienced AL shortening at the 0.0mm/year cutoff, 17.51% at the 0.10mm/year cutoff and 4.61% at the 0.20mm/year cutoff. They also noted significant associations between AL shortening and younger baseline age, female sex and longer baseline AL or greater spherical equivalent refraction. Among those who experienced AL shortening, the mean difference was -0.142mm/year.

"More than a quarter of children experienced AL shortening following at least 12 months of RLRL therapy in this multicenter cohort," the researchers wrote in their paper. "Therefore, RLRL therapy is a proven practical and effective treatment for managing AL elongation and preventing vision-threatening complications."

1. Jiang Y, Zhu Z, Tan X, et al. Effect of repeated low-level red-light therapy for myopia control in children: a multicenter randomized controlled trial. Ophthalmology. 2022;129(5):509-19.

2. Wang W, Jiang Y, Zhu Z, et al. Clinically significant axial shortening in myopic children after repeated low-level red light therapy: a retrospective multicenter analysis. Ophthalmol Ther. January 7, 2023. [Epub ahead of print].

Preterm Children at Greater Risk for Corneal Ectasia

Study shows laser treatment for ROP was associated with further corneal steeping, thinner pachymetry and higher anterior astigmatism.

A positive correlation between retinopathy of prematurity (ROP) severity and corneal steepness has been reported in preterm children, but the role of premature status or ROP pathology in the development of a steep corneal curvature remains unclear. In a study recently published in the journal *Eye*, researchers evaluated corneal topography in full-term and preterm children with or without ROP.

Children aged two to 12 were enrolled in four groups: full-term (77 participants), premature without ROP (178 participants), untreated premature with ROP (45 participants) and laser-treated and/or intravitreal injection of anti-VEGF-treated premature with ROP (131 participants). Corneal topography was measured with the Galilei G4 device, which uses both placido and Scheimpflug imaging, every six months and compared among the groups using generalized estimating equation models at approximately seven years of age.

The study found that premature status led to greater corneal ectasia, and laser treatment for ROP caused further corneal steepness and higher anterior corneal astigmatism.

"Compared with full-term eyes, premature eyes demonstrated steeper anterior corneal curvature, higher anterior and posterior corneal astigmatism and thinner thinnest pachymetry," the authors concluded in their paper. "The laser-treated ROP eyes displayed steeper anterior corneal curvature and higher anterior corneal astigmatism than the intravitreal injection-treated eyes. The laser-treated preterm ROP eyes exhibited high cone location and magnitude index (1.96), reaching the cutoff for detecting keratoconus (1.82)." The authors noted that this was compatible with findings that indicated the premature status led to a greater ectatic cornea (steeper and thinner), whereas laser treatment led to further steepness.

The laser-treated eyes displayed the highest myopia among all preterm ROP eyes, which was possibly attributed to the steepest anterior corneal curvature and smaller anterior chamber depth/axial length ratio, representing a thicker or anteriorly positioned lens.

"Due to significant abnormal corneal topography, premature patients, particularly those with laser-treated ROP, may be suboptimal candidates for laser refractive surgery," the authors wrote.

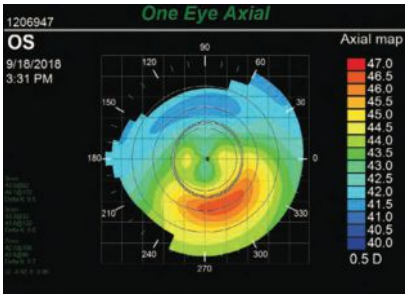


Photo: Oliver Kuhn-Wilken, OD, and Victoria Roan, OD

Preterm children had greater corneal ectasia, and laser treatment for ROP caused further corneal steepness and higher anterior corneal astigmatism.

Wu PY, Chen HC, Hsueh YJ, et al. Corneal topography in preterm children aged 2 years to 12 years with or without retinopathy of prematurity. Eye. December 16, 2022. [Epub ahead of print].

RCCL REVIEW OF CORNEA & CONTACT LENSES

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The Phantom Menace

The effects of neuropathic pain can be tough to track down and handle.

Neuropathic corneal pain is a recently defined condition that is often misdiagnosed and extremely difficult to treat. It is a condition in which corneal pain responds to normal, non-painful stimuli.[1,2] This occurs when nociceptors of the cornea become dysfunctional. Persistent damage and inflammation results in acute nociceptor pain that can transition to chronic neuropathic pain, which is more difficult to manage.[1-3] Increased hypersensitivity to repeated physiological or noxious stimuli develops.[1-3] Central nerves in the brain become hypersensitized and detect pain independent of what is happening to the eye.[4]

Patients can progress to having symptoms of anxiety, depression and apathy.[1] Neuropathic corneal pain has several features in common with conditions such as fibromyalgia and migraines since they share the same hypersensitivity to normal stimuli and the tendency to become chronic.

DIFFERENTIAL CHALLENGES

Unfortunately, there are more questions than answers as to how to diagnose this affliction with certainty. Since impaired corneal nerve function is the hallmark observation, patients often experience a severe sensation of pain/irritation, burning, dryness and light sensitivity. Focal facial dystonia and blepharospasms are not uncommon.[1] There are many known causes for neuropathic corneal pain, including chronic ocular surface disease, post-surgical complications, herpetic infection and toxic keratopathies. Overall, many triggers can lead to corneal nerve damage resulting in corneal neuropathy.[4-6]

As eyecare providers, our job is to decide whether the pain is a result of sensitized peripheral nociceptors or due to a central pain. Applying topical anesthetic can aid in this distinction. If the pain diminishes greatly or goes away entirely, the patient is experiencing peripheral sensitization.[1,4] Applying a soft contact lens or moisture goggles may also neutralize any evaporative component of tear film dysfunction and decrease peripheral pain but not central sensitization.[6] With confocal microscopy, direct evidence of nerve injury can be seen.[1,3,4]

Overall, consider neuropathic corneal pain any time a patient has symptoms that out-distance objective findings ("pain without stain/phantom cornea").[1,4-6] A complete eye examination investigating pain features (chronicity, intensity, systemic connections) is crucial. Use the Ocular Pain Assessment Survey to quantify pain and quality of life impact.[1]

MANAGEMENT

Individualized treatments should concentrate on restoring the ocular surface to minimize inflammation and avoid further nerve insult.[1,3] A stepwise escalation therapy is recommended when a diagnosis is suspected, but once central corneal sensitization has occurred, invasive central pain pathway modulation is necessary.[1,4]

Ocular surface treatment options (artificial tears, systemic and topical antibiotics for blepharitis, sclerals, cyclosporine, topical steroids) are used early in management.[1,3] Neuro-regenerative therapies (autologous serum, nerve growth factor, fibronectin, amniotic membranes) are commonly relied upon. Systemic analgesics, antidepressives and antipsychotics are necessary especially with central sensitization of pain.[1,3] Central pain modulation treatment when intractable also includes electrical stimulation, intrathecal infusions of analgesics, acupuncture and intravenous (IV) immunoglobulin.[1,5] Vitamin B supplements and injection of botulinum toxin have been investigated and appear to also show some promise.[1]

I had a patient who had exhausted nearly all options for her neuropathic corneal pain and has recently started IV immunoglobulin treatment, which seems to help. This has been reported as a good therapeutic option for alleviating pain in various immune-mediated neurologic disorders, with minimal side effects.[5]

Unfortunately, neuropathic pain continues to vex all who deal with it, and there is no one therapeutic approach for every patient. Let's hope IV immunoglobulin might be an effective option. We welcome studies to help determine its efficacy and define appropriate protocols for using it for neuropathic corneal pain. RCCL

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#02 OF SERIES

KERATOCONUS and CROSS-LINKING

Practice Considerations in Managing Keratoconus and Cross-Linking

Nicole Albright, OD
Clinic Director,
Moses Eyecare Center
An independent optometry practice in Merrillville, IN

KEY TAKEAWAYS

- Managing keratoconus (KC) meets patients' needs as part of a medical-model optometric practice.
- There is no global period for cross-linking; each follow-up visit is billed as an office visit.
- The progressive KC patients I have referred for cross-linking have become loyal patients.

Many optometrists are shifting towards a medical model of practice, managing chronic conditions with ocular manifestations, including dry eye, glaucoma, and diabetes. Diversifying the services you offer can better meet the needs of your patients.

Managing keratoconus (KC) is a great way to "lean in" to that more comprehensive medical model of optometric care. About 70% of KC patients first present to an optometrist's office,[1] which means that we have a unique opportunity to identify this progressive disease and refer patients for the FDA-approved iLink® cross-linking procedure in the early stages, before there is permanent vision loss. After treatment, we can continue to address the patient's vision needs over time.

Collaborating with cornea specialists in the care of KC patients has provided comprehensive patient care and strengthened my relationships with ophthalmologists in the community. When they realize that we share a common goal of helping our KC patients, it opens the door not only to specialty contact lens fitting and follow-up care after cross-linking, but to collaboration and referrals in other areas, as well.

Follow-up care after iLink® cross-linking is similar to that required for PRK, with five or more visits and one or more contact lens re-fittings in the first year being typical. After that, KC patients will continue to need vision care and annual medical eye care appointments to monitor for any further corneal changes. While the timing and frequency of office visits may vary by patient and at the doctor's discretion, there is no global period for cross-linking. Any necessary post-treatment visits and diagnostic tests, such as pachymetry and topography, are typically billed separately.

I personally find scleral lens fitting and the management of progressive KC patients who are undergoing cross-linking to be among the most rewarding things I do as an optometrist. First and foremost, we offer them a treatment that can slow or halt KC progression. Furthermore, patients are so very appreciative when you can pinpoint the cause of and address their visual quality problems with contact lenses.

Modeling suggests that iLink® cross-linking saves the average patient nearly $9,000 in direct medical costs and nearly $44,000 in lifetime costs[2]—and that doesn't even include the impact on their mental health and well-being. In addition to the cost savings, it is very fulfilling to me to know that I can help protect a young person with early progressive KC from progressing to the advanced stages of the disease, potentially avoiding a lifetime of vision loss and the need for corneal transplant surgery. One study showed a 25% drop in corneal transplants after the introduction of cross-linking.[3]

Our KC patients are grateful for this care. They will rave about you on social media, refer family and friends—and generally become loyal patients. ■

With your medical management and cross-linking referrals, modeling[2] suggests that patients benefit:

$8,677
DIRECT MEDICAL COST SAVINGS PER PATIENT

$43,759
REDUCTION IN LIFETIME COSTS PER PATIENT

1.88
INCREASE IN PATIENT QUALITY-OF-LIFE-YEARS

REFERENCES:
1. Eisenberg JS. First Treatment for Keratoconus Itself. Optometry Times, June 1, 2012. 2. Lindstrom RL et al. J Med Econ 2021;24:410. 3. Godefrooij DA, Gans R, Imhof SM, et al. Acta Ophthalmol 2016; 94:675-678.

SCAN WITH PHONE
Learn more about iLink corneal cross-linking here

iLink® CROSS-LINKING PROCEDURE

Sponsored by Glaukos

GLAUKOS TRANSFORMING VISION

By Becky Su, OD, Marcus R. Noyes, OD, and John D. Gelles, OD

A Balancing Act

Here's how to equalize vision for a patient with asymmetric keratoconus.

A 33-year-old male presented to the clinic with a history of keratoconus, forme-fruste in the right eye and moderate in the left, made even more challenging by his career as a pilot. The left eye was treated with corneal crosslinking about one year ago. The patient had a history of soft lens intolerance in the left eye, which was currently corrected with a scleral lens. He reported discomfort and rebound redness with his habitual scleral lens. Notably, he reported that despite scleral lens wear, visual quality of the left eye was poor compared with the right. His goal was to have similar visual quality in both eyes.

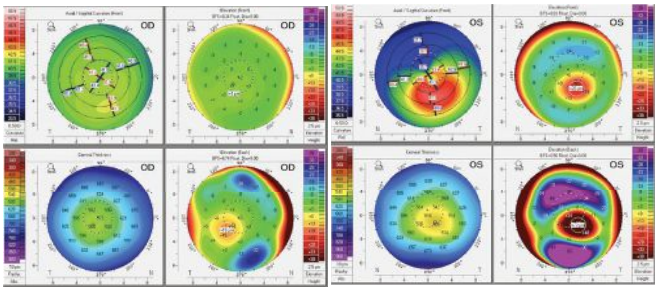
On initial presentation, uncorrected visual acuity was 20/20 OD and 20/40 OS. Visual acuity with his habitual scleral lens on the left eye was 20/20. Best-corrected visual acuity (BCVA) was 20/20 in each eye, with a manifest refraction of +0.25-0.50x090 OD and +0.25-4.25x120 OS.

Scheimpflug tomography (Pentacam Wave AXL, Oculus) showed maximum keratometry readings of 41.9D and 48.2D and IS ratios of 1.5D and 10.5D in the right and left eyes, respectively. On the slit lamp exam, large nasal pingueculas were documented on each eye. With the current scleral lens, there was significant impingement on the pinguecula during lens wear, and upon removal, there was a deep lens impression and grade three injection of the conjunctiva at the pinguecula.

CONSIDERATIONS

Here, we highlight our thought processes and consider how each of us would proceed in this situation:

Dr. Su. Aviation has strict visual requirements since pilots must navigate difficult and dynamic conditions. Crisp vision is a must. Although this patient can achieve 20/20 vision with glasses, it is not surprising that the amount of irregular astigmatism from the left eye would result in glare, halos and ghosting images. These visual disturbances could have dangerous consequences, especially while flying.



Corneal tomography of the patient's right and left eyes.

A modality such as a rigid gas permeable (RGP), hybrid or scleral lens could provide the optics needed for crisp vision. However, consideration needs to be taken for the patient's lifestyle and occupation. Since he is sometimes required to fly for long periods in a dry environment, an RGP or hybrid lens may not give him comfort or visual stability compared with a scleral lens. In this case, a scleral may be the right choice to help him achieve his goals.

Additionally, the patient reported residual glare and streaking of images from his habitual scleral lens, most likely due to the residual higher-order aberrations (HOAs). With wavefront-guided scleral lens technology, we can further reduce the residual glare/flare/halos with HOA-correcting optics incorporated on the front surface of the scleral lens. These high-performance optics would reduce the amount of shadowing, resulting in a similar visual experience in both eyes.

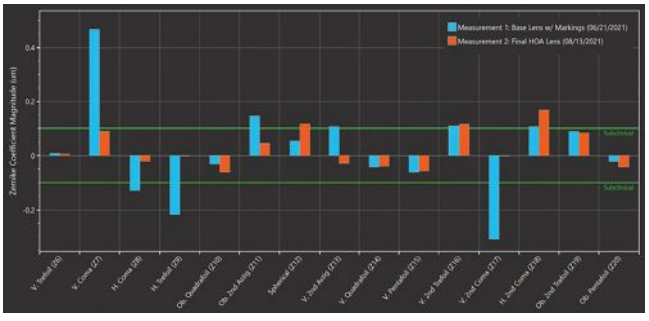
A common challenge to successful scleral lens wear is the presence of a pinguecula. The lens haptic can cause compression and mechanical damage to the tissue, resulting in redness and discomfort. For some patients, reducing the lens diameter to minimize the interaction of the lens edge with the lesion is the simplest option. Nonetheless, this may be more difficult in patients with moderately large pingueculas or those close to the limbus. More complex options include edge notching—removal of lens edge material—to avoid the pinguecula. Careful follow-up is still needed to ensure the conjunctival tissue around the notch does not impinge and desiccate over time. Some scleral lens designs can incorporate a micro elevation to contour the edge over the pinguecula without compression. Custom impression-based or scan-based scleral lenses may provide the best fit and comfort for this patient, as ocular surface data takes into account all the elevations and contours of the cornea and sclera. This can be mirrored and manufactured onto the lens haptic.

Dr. Gelles. Patients with asymmetric keratoconus can be some of the most challenging, especially when the less affected eye is nearly emmetropic. Adequate uncorrected vision

of the emmetropic eye can make monocular contact lens wear a chore. These patients are often hyper-aware of the lens. For monocular wear, I tend to use soft and scleral lenses over other options as they are usually associated with less lens awareness.

Another challenge is visual quality. Even with correction, the more severe eye may still not be on par with the better eye due to residual aberrations. To address visual quality complaints, wavefront-guided optics can provide a solution. These are currently available but only on select scleral lens designs. Research shows a 40% to 60% reduction in HOAs, and our clinical experience mirrors these numbers. Add a large pinguecula and you have a real challenge.

In this case, there is also a mental aspect to consider. The patient is already wearing a scleral lens, which is not meeting his needs. A previously poor experience can make trying the same contact lens modality again challenging. An impression-based scleral lens with wavefront-guided optics may be the best choice in this situation. It's important to explain the lens differences so there is an understanding that though we will be using another scleral lens, it will be nothing like the current.



Aberrations of the standard scleral lens (base lens) vs. the wavefront-guided scleral lens (final lens) in the left eye.

Dr. Noyes. Any case where the patient's subjective vision does not line up with their visual acuity is difficult, especially when they are reading close to 20/20 or better. In this specific situation I'd tell the patient, "You don't have to wear your scleral lens all the time, but you do have to wear it while you're flying." Many of these patients will find it cumbersome to wear a lens when they can complete their daily tasks without them. It's important to keep the patient's lifestyle in mind when fitting them in scleral contact lenses. If for some reason vision is not satisfactory with scleral lenses, new advancements such as HOA correction provided by wavefront-guided optics are now an option.

DISCUSSION

Complex ocular geometries and conjunctival elevations, such as pingueculas, can cause trouble with scleral lens wear. Modifying the lens haptic with advanced options to contour over these obstacles will ensure comfortable and healthy lens wear over time. To evaluate the visual potential and quality of the worse eye, a rigid lens over-refraction must be done. If vision improves and residual glare is resolved with an over-refraction, the over-refraction can be incorporated onto the front surface of the scleral lens, and the optics can be finalized. If the glare is not fixed, the problem primarily lies in residual HOAs. Wavefront aberrometry over the scleral lens will quantify the type and amount of residual aberration.

An integrated wavefront aberrometry system now exists, which can measure the amount of residual HOAs and turn them into a wavefront-guided optical profile on the lens. Once manufactured and worn, this will reduce residual aberrations and lead to improved quality of vision. Incorporating new technological advancements such as this and working with the necessary labs can help your patient achieve their desirable clear and comfortable vision in both eyes.

RESULT

The patient was refit with an ocular impression-based scleral lens (EyePrintPro, EyePrint Prosthetics) on the left eye. Importantly, he was directed to discontinue lens wear for one to two weeks to allow the conjunctival tissue to return to its natural shape. On follow-up, he presented with 20/15 OD and 20/30 OS visual acuity, with a BCVA of 20/20 in the left eye with a spherical-cylindrical over-refraction. HOA-correcting optics were ordered via a wavefront aberrometry system (xWave, Ovitz).

On further follow-up, he presented with 20/15 visual acuity in the right and left eyes. The residual HOA was reduced by 53% after incorporating the HOA-correcting optics onto the front surface of the lens. The patient was delighted to have equal vision in both eyes and significantly improved quality of vision in the left eye during his flights. RCCL

Dr. Su is the Cornea and Contact Lens Fellow at the Cornea and Laser Eye Institute (CLEI) Center for Keratoconus. She has no financial interests to disclose.

Understanding the TEAR FILM

Let's dissect each layer and its importance, along with the variety of elements that compromise it.

By Rebecca Rojas, OD

Dry eye, like many other conditions, has been extensively studied for decades. As the cases of symptomatic patients continue to increase, a considerable amount of research has been done to better understand the ocular surface and tear film.

In 1995, the National Eye Institute provided one of the first global definitions, etiologies and classifications of dry eye. At that time, dry eye was defined and recognized as a "disorder of the tear film due to tear deficiency or excessive tear evaporation."[1] Since then, the definition has been reviewed and revamped through better understanding of the pathophysiology. A recent tear film subcommittee DEWS II report added changes to the definition to state that dry eye is a "multifactorial disease" that results in tear film instability, inflammation, hyperosmolarity of tears and the effect neurosensory components have on dry eyes.[2]

The tear film covers the cornea, bulbar and palpebral conjunctiva and is composed of three layers—the lipid, aqueous and mucin layers, although the TFOS DEWS II report has argued for combining the aqueous and mucin layer into the muco-aqueous layer.[3] The disruption to any of these layers or a combination of them will lead to an abnormal and unhealthy ocular surface.

There are several functions of the tear film, including maintaining a smooth surface for refraction of light, lubrication of the ocular surface, supplying the avascular cornea with nutrients, removing foreign materials from the cornea and conjunctiva, and protecting the eye from pathogens.[4]

Tear film instability can be associated with a wide range of factors. Abnormalities or problems with the tear layer lead to loss or insufficient supply of tear film to environmental and external factors such as incomplete lid closure, malposition or lagophthalmos. An incomplete blink or lid malposition leads to inadequate lipid distribution over the tear film and areas of exposure have increased evaporation. Therefore, external factors including long-term contact lens wear, increased hours or prolonged use of digital devices can also lead to lipid deficiency.[5]

Here, we will discuss the pathophysiology of factors that affect the tear film. Proper knowledge of what causes patients' symptoms will help make you make the right decisions on treatment for each specific patient.

LIPID LAYER

This is the outermost layer that serves as the connection and barrier from the ocular surface to the environment. Besides serving as a barrier, the lipid layer provides tear film stability by reducing surface tension and allows meibum secreted by meibomian glands and tear lipids to spread with each blink. This creates a smooth optical surface for optimal vision. It also limits contamination from microorganisms and helps prevent tear evaporation.

The lipid layer is produced by meibomian glands, glands of Moll and Zeiss and epithelial cells. It is approximately 40nm to 60nm thick and can be further divided into different classes of lipids categorized into outer and inner layers. The outer lipid

ABOUT THE AUTHOR

Dr. Rojas is an instructor in optometric science (in ophthalmology) at Columbia University Medical Center. She received her undergraduate degree from the University of Central Florida and graduated from Nova Southeastern College of Optometry. She completed her optometric residency in ocular disease at SUNY College of Optometry. She specializes in medically necessary contact lens fittings and dry eye, and comanages refractive, corneal and ocular disease. She has no financial disclosures.

layer, known as the lipid-air interface, is composed of non-polar lipids such as cholesterols, triglycerides and free fatty acids. The inner layer, which makes up a smaller portion of the lipid-aqueous interface, is composed of ceramides, phospholipids and cerebrosides, known as polar lipids.[6]

The most common reason for lipid layer dysfunction is due to Meibomian gland dysfunction (MGD), which can be associated with a variety of systemic and ocular conditions, along with environmental factors and medications. External factors such as use of makeup eyeliner result in obstructive MGD, gland dropout, microtrauma and possible toxicity over time, resulting in progressive gland damage and then gland loss.[7]

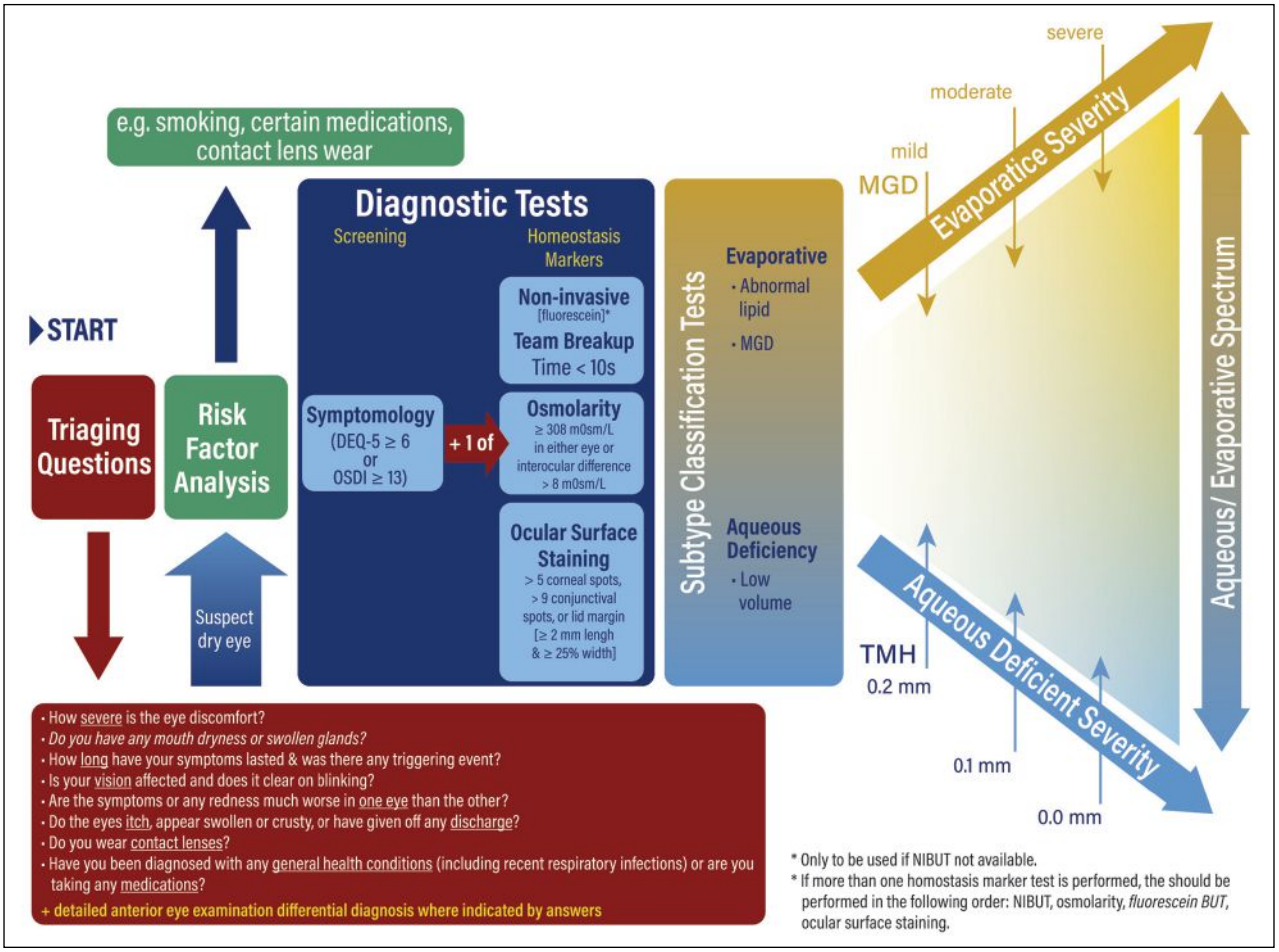
AQUEOUS LAYER

This layer is produced by the lacrimal gland mainly with contributions from goblet cells and accessory lacrimal glands. The main lacrimal gland is also responsible for reflex tearing. This layer is about 8mm thick and represents the bulk of the tear film. It's important for lubrication, protection (by washing away contaminants and foreign bodies) and nourishing the avascular cornea. The aqueous layer includes proteins, immunoglobulins, glycoproteins, growth factors, vitamins and electrolytes important for ocular surface health.

Aqueous-deficient dry eye is associated with the lack of lacrimal gland secretions due to dysfunction or blockage of the glands, and is divided into Sjögren's dry eye and non-Sjögren's dry eye. Sjögren's syndrome is an autoimmune condition associated with exocrine gland dysfunction, involving the salivary and lacrimal glands and results in dry eyes and dry mouth.[8] It can be present solely as a primary diagnosis or secondary with other autoimmune associations such as rheumatoid arthritis or systemic lupus erythematosus.

In non-Sjögren's dry eye, reduced aqueous can be due to several factors involving the lacrimal gland, which range from lacrimal duct obstruction or damage, conjunctival damage due to trauma or scarring (*e.g.*, cicatricial pemphigoid, trachoma) and aging.

Any external factor that alters the composition of the aqueous will result in a compromised aqueous



The TFOS DEWS II dry eye diagnostic algorithm at a glance.

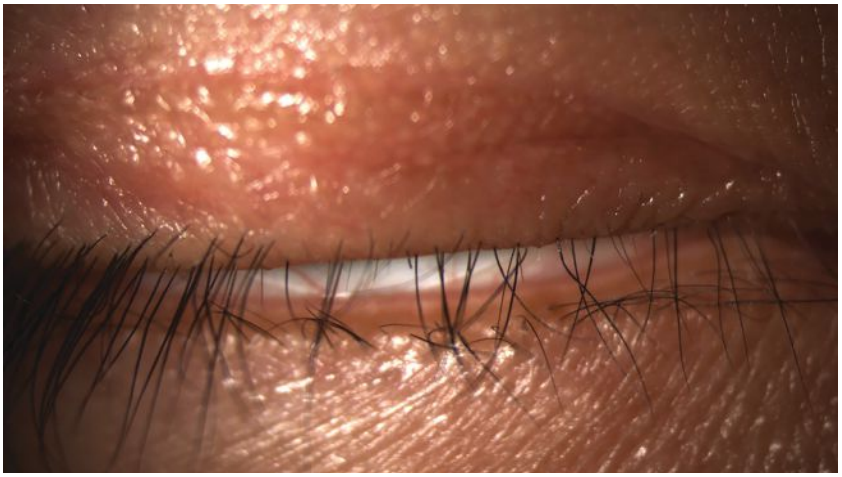


Photo: Irene Frantzis, OD

Lagophthalmos can cause inferior corneal exposure and contribute to DED.

layer, turning into dry eye. Studies have shown that loss of growth factors associated with ocular surface disease or inflammation, increased electrolytes measured in tears (evaporation or exposure) and presence of proinflammatory cytokines will lead to disruption in the tear film.

When there is scant aqueous production, the ocular surface will have a reduced tear lake or high tear osmolarity. This is based on the amount of electrolytes in the aqueous layer, largely produced by the main and accessory lacrimal glands (Krause and Wolfring) from the cornea and conjunctiva.[9] Tear hyperosmolarity is caused by reduced aqueous tear flow or increased evaporation of aqueous tear layer. With high tear osmolarity there is associated apoptosis of corneal, conjunctival and mucin-producing goblet cells.[10] Therefore, patients with aqueous deficiency will have hyperosmolarity of the tear film, a reduced tear lake, Schirmer testing of less than 10mm and diffuse sodium fluorescein staining pattern.[11]

MUCIN LAYER

This layer is important in stabilization of the tear film by making it hydrophillic and allowing the aqueous to spread over the ocular surface. Although it is suggested to be the thinnest layer of the three, the mucin layer plays a significant role in allowing the tear film to adhere to the surface by the gel-forming mucins and trapping and clearing contaminants and debris. Mucins are produced primarily by the goblet cells and apical cells of the cornea, conjunctiva and lacrimal gland.

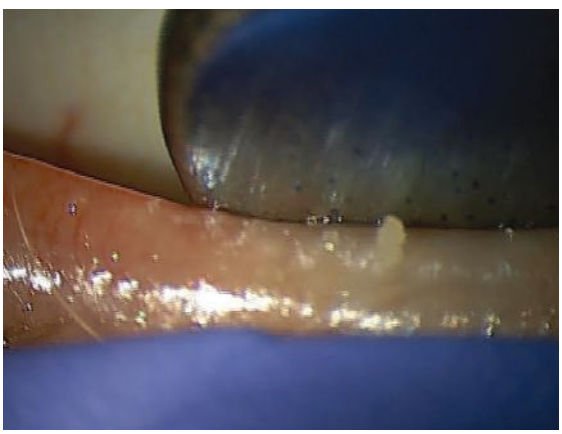
Mucin deficiency is associated with conditions that have goblet cell damage, such as ocular cicatricial pemphigoid, Steven-Johnsons syndrome or other conjunctival disorders, and with vitamin A deficiency.[12] Xerophthalmia is caused by severe vitamin A deficiency with the most common causes attributed to malnutrition or malabsorption due to poor diets, alcoholism, gastrointestinal, pancreatic and liver diseases.[13]

COMPROMISES TO THE TEAR FILM

Each layer works independently but functions collectively as a unit to support the ocular surface and, similarly, can be damaged by conditions and external factors affecting all layers at once.[14] These conditions include:

Aging. Increased aging results in tear film instability, decreased lacrimal secretion, increased evaporation rate, changes in lid apposition, conjunctival changes and change in tear film composition.[15] Anatomical and physiological changes include atrophy or dysfunction of the lacrimal and meibomian glands, decreased nerve fiber density and long-term inflammation by infections or surgeries leading to decreased corneal sensation.

It is still unclear what exactly causes the changes in tear film composition, but some recent studies have shown tear film property differences between young and adult comparisons, including a decrease in antimicrobial lysozyme, lactoferrin and IgA proteins in the tears, with an increase in IgG, ceruloplasmin and other inflammatory interleukins and proteins in tears.[16] Conjunctivochalasis has also been associated with causing instability of the tear film with aging. The exact etiology is not understood, but the tear film instability is likely due to the redundant conjunctival folds that decrease tear drainage and outflow and in turn release inflammatory MMPs from repeated friction with every blink.[17]



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A patient with DED associated with MGD showing poor MG expression.

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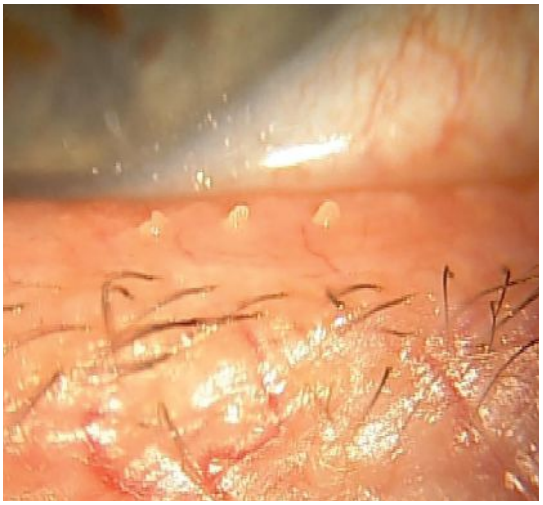
Infection. Another one of the tear film's functions is to provide a protective barrier from external factors such as microorganisms and bacteria. The tear film has several antimicrobial proteins produced by the lacrimal gland and corneal and conjunctival epithelial cells.

Proteins such as lysozyme, lactoferrin, lipocalin and secretory immunglobulin A produced by the lacrimal gland and found in the aqueous layer provide bacterial and antifungal protection, with lysozyme being the most abundant protein. Secretory immunoglobulin A is one of the primary antibodies in tears and functions to remove and clear pathogens from ocular surface.[18] In aqueous-deficient dry eye, these proteins are reduced, leading to increased susceptibility of infections. When infections occur, there are changes to these antimicrobial enzymes resulting in decreased tear break up time, more tear instability, and more reflex tearing (due to increased aqueous secretion).

Contact lens wear. There are several theories regarding changes to the tear film with contact lenses. Their use can promote increased tear evaporation, altered mucin production and reduced oxygen, as well as affect the concentration and lipids and proteins present in the tear film. Contact lenses are thought to disrupt the tear film by isolating the mucin layer behind the lens from the pre-lens lipid layer and impacting the natural congruity of the tear film layers.[19] This disruption may lead to a reduced amount of antimicrobial proteins and make the ocular surface more susceptible to infections and inflammation.

It's been noted that long-term wear of contact lenses, especially GP lenses, can decrease Müller's muscle, leading to less or incomplete blinking which in turns leads to lipid layer deficiency and subsequent dry eye.[20]

Photo: Paul Karpecki, OD



Another MGD patient that likely suffers from chronic tear instability resulting from inadequate lipid release to the ocular surface.

Drugs. There are various medications that affect the tear film through different mechanisms, such as producing changes in the lacrimal gland, medications being secreted in the tears or systemically affecting overall secretions in the body. Over-the-counter painkillers, diuretics and chemotherapeutic agents can worsen dry eyes.

Many systemic medications that affect the tear film include anticholinergic drugs that have antimuscarinic effects. Antimuscarinics work by blocking muscarinic receptors from binding to the cholinergic receptors, which in turn lead to bronchodilation, mydriasis and inhibiting secretions, affecting the tear film. The cause of dry eye through this mechanism is decreased production of aqueous and mucin layer from the lacrimal and goblet glands respectively, leading to instability of tear film. Some of the most common medications associated with anticholinergic mechanisms that lead to decreased aqueous outflow are anxiolytics, antipsychotics, antidepressants, narcotics, and antihistamines and decongestants. Beta blockers in hypertensive medications also reduce aqueous production, leading to dry eye, while other medications such as topical isotretinoin or topical glaucoma eye drops can lead to meibomian gland dysfunction. Hormones, such androgens, TSH and estrogens, have been noted to influence lacrimal gland production or mucus secretion but require more studies to confirm.

Injury and/or ocular surgery. Changes in the tear film associated with ocular surgery include corneal nerve damage due to surgical incisions that reduce or disrupt tear production by damaging nerve fibers and corneal sensitivity and can lead to inflammation of the ocular surface. Light exposure and exposure to free radicals have also been questioned in causing damage to the corneal and conjunctival epithelial cells. (No significant data has confirmed this, but studies have noted decreased TBUT or Schirmer's testing postoperatively that have either improved over time or remain slightly decreased).[21] Blepharoplasty changes the position of the lids and can lead to tear film evaporation, while incisions cause surface irregularities or decreased mucin production resulting in compromised tear film.

Environmental influences. This includes low humidity, high altitude, pollution, wind, dust and allergens, all of which compromise the ocular surface. The quality of air and exposure to pollutants and allergens affects tear film stability and has been noted to be associated with increased inflammatory cytokines and MGD. Patients who live in cities with higher pollution levels or work in environments with increased dust, mold and smoke are more symptomatic to dry eyes due to increased TBUT by oxidative stress and inflammation. Similarly, patients living in certain regions or geographical locations with lower humidity or higher altitude are more susceptible to

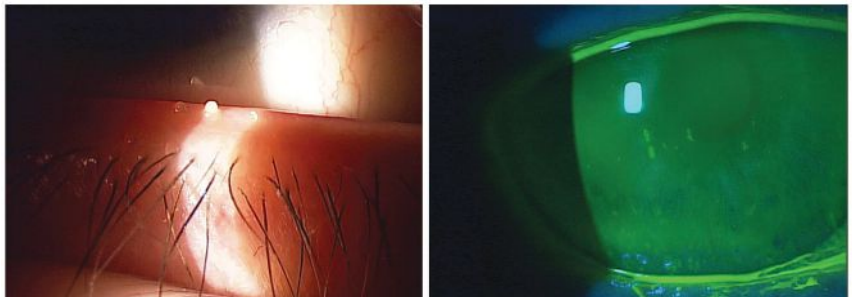


Photo: Paul Karpecki, OD

Evaporative DED, a consequence of MGD (left), and aqueous-deficient (right), are the two primary types of dry eye.

dry eye due to disruption of the ocular surface, resulting in increased tear film osmolarity and decreased TBUT.[22]

TAKEAWAYS

Dry eye disease is a common, chronic condition. Since it is multifactorial in nature, an accurate diagnosis can be challenging but necessary for the most appropriate treatment. A stable tear film is important for a healthy ocular surface and, over the years, there have been several advances and insights into factors that affect ocular surface health.

As more studies are conducted, further understanding of the biochemistry and pathophysiology of the tear film will enhance diagnosis and treatment options to optimize homeostasis of the ocular surface for symptomatic patients. Because dry eye symptoms can be difficult to treat, educating patients on factors compromising the ocular surface can help with compliance as they incorporate lifestyle modifications to aid in maintaining a healthy, stable tear film. RCCL

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The Epithelium in Distress: From RCE to Dystrophy

To provide comprehensive patient care, optometrists must have a clear understanding of the function and pathophysiology of this structure.

By Karen K. Yeung, OD, and Rachel Snyder

The corneal epithelium, which is a mechanical, immunological and biological barrier to the outer environment, is only five to seven uniform cell layers deep and 50µm thick. Disruption of the epithelium from injuries, dry eyes, allergies, infectious and noninfectious entities and corneal dystrophies can lead to clinical diseases that compromise the health of the entire cornea. Fortunately, damage to the corneal epithelium, as long as it does not extend below Bowman's layer, will not cause scarring or permanent visual loss once resolved.

This article will highlight the various issues that can arise—from recurrent corneal erosions (RCEs) to dystrophies—and lead to epithelial stress and possibly vision loss. Though many ocular conditions penetrate deeper than the epithelium, only the pathophysiological effects on this structure will be discussed.

EPITHELIAL STRUCTURE

The epithelium is comprised of three layers: apical cells, wing cells and basal cells. The corneal epithelium undergoes involution, apoptosis and desquamation every seven to 10 days, which plays a large role in shedding infected cells from the corneal surface.[1]

Apical cells. This superficial aspect is two to three layers of flat polygonal, non-keratinized squamous cells. On their anterior surface are microplicae and microvilli, which extend up to 0.5µm into the tear film, hence increasing the surface area. Coated with a dense glycocalyx, apical cells help stabilize the surface tear film. Desmosomes form tight junctions between the superficial layer cells, creating a selective barrier to substances in the tear film.[2]

Wing cells. Below the superficial layer are two to three layers of wing cells that adhere together by desmosomes and adherens junctions. They have gap junctions that allow molecules to be exchanged directly between cells.

Basal cells. Below the wing cells is a single layer of columnar cells forming the basal epithelium, which adheres the epithelium to Bowman's membrane. They are the source of wing and apical cells, since they are the only corneal epithelial cells that are capable of mitosis. The corneal epithelium self-regenerates, turning over all of the cells in approximately five to seven days.

CORNEAL ABRASIONS, RCEs

Superficial abrasions in the cornea can be caused by trauma, foreign body insult, including contact lenses (CLs), or spontaneously. They are common across all age groups and responsible for 3% of eye concerns in primary care clinics.[3] Scarring of the cornea will not occur unless the abrasion reaches below Bowman's layer. Upon slit lamp evaluation, topical positive fluorescein stains any irregular, loose or missing epithelium from an abrasion. Any negative staining represents elevations on the epithelium.

Corneal abrasions, sometimes years later, can abrade again as RCEs. In fact, 45% to 64% of RCEs occur after corneal trauma to the superficial cornea. The next most common cause of RCE is epithelial basement membrane dystrophy (EBMD), with 19% to 29% of these patients having RCE.[4] The highest prevalence of EBMD is in adults between 30 and 40 years old; however, it also affects those between 30 and 80 years of age.[5] Furthermore, there is also a high rate of RCE in individuals with dry eyes, diabetes, blepharitis, ocular rosacea, other corneal epithelial dystrophies and corneal degenerations.[5,6]

ABOUT THE AUTHORS

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RCE is associated with a sudden onset of pain, especially upon wakening. Ocular desiccation from sleeping with the eyelids closed causes adhesions between the tarsal conjunctiva and corneal epithelium. When the eye opens, the shearing force of the eyelids avulses the corneal epithelium from the epithelial basement membrane due to the weakened or dysfunctional hemidesmosome attachment between the epithelium and the basement membrane.[5,7] Primarily unilateral (unless accompanied by a dystrophy) symptoms lasting from minutes to hours may include photophobia, redness, blurred vision and tearing. Persistent corneal defects may last for days, though neurotrophic keratitis should be considered in epithelial defects that last 10 or more days even with palliative treatment.[8] Slit lamp findings may show conjunctival injection, epithelial defects or corneal signs indicative of a corneal dystrophy (*e.g.*, map-dot-fingerprint for EBMD).

KERATITIS

An inflammation of the cornea from both infectious and noninfectious etiologies, keratitis can be localized or systemic. It is generally associated with corneal edema, infiltration of inflammatory cells and ciliary congestion. Noninfectious etiologies include those from dry eyes, allergies and neurotrophic corneal disorders. Infectious organisms include viruses, bacteria, protozoa, parasites, fungi and oomycetes. Most organisms cannot penetrate an intact epithelium, so many infections occur with the presence of epithelial damage or compromise. There are a few extremely virulent organisms, including *Neisseria gonorrhea*, *Haemophilus aegyptius*, *Corynebacterium diphtheriae*, *Bacterium diphtheria* and *Listeria* species, that can penetrate an intact corneal epithelium resulting in severe corneal insults.[9]

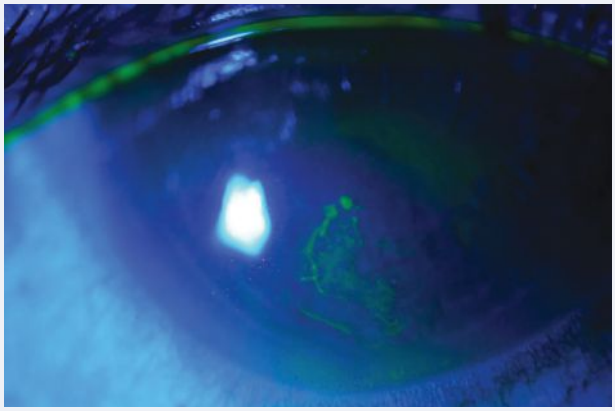

Photo: Rebecca Rojas, OD

Pictured in this eye is an RCE.

Pseudomonas and *Staphylococcus* are the most common causes of keratitis in CL wearers, followed by *Acanthamoeba*. Fungal and viral corneal infections are generally not specific complications of lens wear. Factors that contribute to CL-related keratitis include extended wear, overwear, corneal hypoxia, poor lens hygiene, rinsing of CLs in tap water, swimming in lenses, lens-induced corneal trauma and cellular toxicity from multipurpose CL solutions.[10,11] The severity of the infection is dependent on the pathogenicity of the microbe, the underlying condition of the cornea and the individual's immunological state. After breaching the epithelium, the pathological microbes can cause keratitis and invade the stroma.

It is important ODs recognize both noninfectious and infectious etiologies of keratitis. We will first discuss the various noninfectious causes that may present in optometric practice.

Dry eyes. Depending on the population, dry eye can affect 5% to 35% of individuals.[12] It can be caused by a myriad of conditions including dry/drafty environments, CLs, eye drop preservative toxicity, prolonged computer use, post-LASIK and systemic medications.

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- Recognize the pathophysiology of this structure.
- Describe a healthy epithelium and how it functions.
- Discuss the various conditions that can impact the epithelium.
- Identify when a patient's epithelium is in distress.

Target Audience: This activity is intended for optometrists engaged in managing patients with epithelial damage.

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The resultant tear hyperosmolarity triggers an inflammatory event that causes the protease-mediated lysis of tight junctions between the epithelial cells and eventual cell apoptosis.[13,14] The epithelial surface becomes irregular, and areas of desiccation cause sensitization of epithelial nociceptors. In chronic dry eyes, the areas of desiccation appear as superficial punctate keratitis (SPK) with sodium fluorescein staining. The corneal epithelium becomes thinner as the density of its three layers decrease.[15] Epithelial cells also become enlarged and irregularly shaped. Individuals report foreign body sensation with their dry eyes.

Things That Affect the Epithelium

Injury

- **Corneal abrasion**
- **RCEs**

Keratitis

- **Noninfectious**
  - Dry eye disease
  - Thygeson's SPK
  - Allergies
  - Neurotrophic corneal ulcer
- **Infectious**
  - Viruses
    - HSV, VZV, adenovirus and others
  - Bacteria
    - *Pseudomonas*, *Staphylococcus*, *Streptococcus*, *Moraxella*, *Nocardia* and atypical *Mycobacteria*
  - Protozoa
    - *Acanthamoeba*
  - Fungal
    - *Aspergillus*, *Fusarium*, *Candida* (yeast), *Cladosporium*, *Alternaria*, *Curvularia* and *Microsporidia*
  - Oomycete
    - *Pythium*

Epithelial/Subepithelial Dystrophies

- **EBMD**
- **ERED**
- **SMCD**
- **MECD**
- **Lisch epithelial corneal dystrophy (not discussed here)**
- **Gelatinous drop-like corneal dystrophy (not discussed here)**

Thygeson's SPK. This condition appears as one to 50 multiple bilateral, intraepithelial, elevated, whitish-gray, granular-looking corneal epithelial lesions in the center of the cornea. Some of the opacities have a raised center that breaks through the epithelial surface as evident with sodium fluorescein staining, which is the main cause of foreign body sensation, photophobia and slightly reduced vision. Thygeson's SPK is chronic with multiple insidious onsets, long durations without serious sequela and remissions.[16] During remissions, the opacities may completely disappear unless there is subepithelial scarring that does not stain with fluorescein.[17] The etiology of Thygeson's remains unknown.

Allergies. Allergic conjunctivitis affects up to 40% of the US population, and 30% of these individuals have corneal involvement.[18] Allergies affecting the cornea occur from the loss of barrier function of the corneal epithelium.[19] These patients have an altered organization of the tight junctions and abnormal expression of junctional proteins. This allows allergens to cleave the tight junctions between superficial epithelial cells and penetrate the paracellular space, eliciting the strong innate immune response and the chronic inflammation/corneal swelling that generally occurs with allergies. Clinically, symptoms include itchy eyes, foreign body sensation and tearing.

Neurotrophic keratitis. Any ocular or systemic condition that damages the trigeminal nerve (cranial nerve V) or the corneal nerve plexus can cause neurotrophic keratitis. Etiologies may include herpetic keratitis, trigeminal nerve damage caused by orbital or head injury, surgery, strokes, chemical burns, physical injuries, corneal surgeries, chronic medication use and CL wear.[20,21] Other causes may be from systemic disease such as diabetes, leprosy, multiple sclerosis and intracranial masses that affect the trigeminal nerve such as aneurysms, meningioma and schwannoma.[21]

The corneal epithelium is highly innervated, and any decreased corneal nerve sensitivity can result in corneal surface desiccation, SPK, persistent epithelial defects and ulcers that can progress to stromal melting and corneal perforation.[21] Animal models have shown that within hours of ocular nerve damage, the apical epithelial cells swell, lose their microvilli surface and slough off at a rapid rate into the tear film.[22] The cornea thins, and there is also decreased epithelial wound healing, and the new epithelium is prone to RCEs.[23]

As previously mentioned, there are also a number of infectious etiologies of keratitis. These are discussed in more detail below.

Viruses. Common viruses that can affect the corneal epithelium include herpes simplex virus (HSV), varicella zoster virus (VZV) and adenovirus. As the first line of defense, corneal epithelial cells initiate the corneal immune response by releasing proinflammatory cytokines and chemokines to recruit mononuclear lymphocytes and neutrophils into the cornea. Epithelial cells also produce interferons to enhance antiviral activities.

While HSV1 involves the cornea through direct contact, HSV2 can be transmitted to the eye through infected venereal secretions. In both HSV1 and 2, the primary infection rarely involves the cornea, but unfortunately this is when the virus is carried to the ophthalmic branch of the trigeminal ganglion and becomes latent. Similarly, VZV's primary infection causes chickenpox, but following the primary infection it establishes latent infection in neuronal cells in the peripheral ganglia and affects the cornea if the ophthalmic branch is involved. Both

HSV and VZV can be latent in the same ganglion.[24] Reactivated latent virus can result in corneal infection when the latent virus becomes reactivated, resulting in shedding of the virus on the corneal surface. Reactivation can cause epithelial dendritic or geographic keratitis.

Among adenoviruses, epidemic keratoconjunctivitis (EKC) is the only form of adenovirus that can affect the cornea. However, it is also highly contagious and causes severe keratitis. Adenoviruses are robust, resilient to standard disinfection methods and easily transmitted in high-density populations. They spread via droplets through the respiratory tract or eye or by a contaminated medical device/unclean surface through viral shedding. While most adenovirus infections are self-limiting, the keratitis can persist or recur months to years after the initial infection. EKC presents with punctate or large, geographically-shaped epithelial erosions that typically resolve in several days.[25] Unfortunately, 60% of EKC infections will reach the stroma and cause stromal keratitis.[26]

Bacteria. With the increase of CL use over the past few decades, the rate of bacterial keratitis has increased proportionally.[27] Fortunately, single-use CLs are becoming more prevalent. With the lowest rate of environmental organism adherence, they have protective effects from infections.[28]

Bacterial keratitis is a major cause of sight-threatening emergencies once the epithelium is breached.[29] A majority of bacterial keratitis cases arise from *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa* and species of the *Enterobacteriaceae* family (including *Klebsiella, Enterobacter, Serratia* and *Proteus*). The ocular pathogenicity of different types of bacteria is related to their ability to adhere to and invade corneal epithelial cells.[30] *Pseudomonas aeruginosa* is the most frequent cause of bacterial keratitis and is also the most pathogenic, with the capability of corneal perforation within 72 hours. The keratitis has a "ground glass" appearance.[31]

Gram-positive bacteria have fibrillae, and gram-negative bacteria have fimbriae and glycocalyx that adhere to specific proteins on the damaged corneal epithelium. After adhering to the epithelium, they release proteases and exotoxins that cause the basement membrane to degrade and to penetrate and lyse the epithelial cells. In the meantime, the bacteria multiplies and invades the stroma. After active ulceration, the inflammatory response regresses, resulting in cicatrization if the infection breached Bowman's layer.

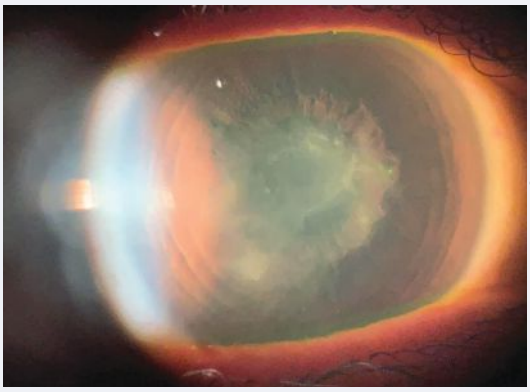

Photo: Cecelia Koetting, OD

A corneal scar from HSV with a persistent epithelial defect after a corneal erosion.

The different bacteria have characteristic clinical ocular presentations. Gram-positive bacteria tend to produce small distinct abscess lesions. *Staphylococcus aureus* bacterial keratitis presents with suppuration and yellow-white opaque deep stromal abscesses. *Staphylococcus epidermidis* keratitis may also have stromal abscesses but not to the severity of *Staphylococcus aureus*.[32] *Streptococcus pneumoniae* corneal infections appear as central oval stromal ulcers with a progressive edge while another edge is healing. They cause posterior corneal abscesses and anterior chamber hypopyon. Gram-negative bacteria cause diffuse, rapidly spreading necrotic lesions.

Pseudomonas aeruginosa has a characteristic greenish-yellow discharge with severe inflammation and a rapidly progressing ulcer that may be accompanied by stromal melting, infiltrative rings, hypopyon and endothelial plaque. *Klebsiella* keratitis has whitish-gray pleomorphic suppuration with a diffuse stromal haze. *Moraxella* causes severe oval stromal ulceration with a necrotic edge, corneal perforation, mild to moderate anterior chamber reaction and hypopyon.[33] *Neisseria gonorrhea* ocular infections present with hyperpurulent conjunctivitis, chemosis and a rapidly progressive stromal infiltration.

Protozoa: Acanthamoeba. This is a common free-living protozoan amoeba that resides in soils and unchlorinated bodies of fresh water. *Acanthamoeba* can cause sight-threatening keratitis in both non-CL wearers and CL wearers, comprising 5% of lens-related keratitis.[34] *Acanthamoeba* keratitis (AK) affects non-CL wearers who are regularly exposed to dust, soil or contaminated water.[35,36] In lens wearers, AK occurs through poor lens hygiene, swimming with CLs, washing lenses in tap water, topping off CL solutions and using ineffective lens solutions.[10,37]

The adherent surface of soft lenses allows *Acanthamoeba* access to the cornea. Trophocytes adhere to the increased expression of mannose glycoproteins on the surface of injured corneal epithelium.[38] Once attached, they release proteases that are extremely cytolytic to the corneal epithelial cells. They also rapidly encyst themselves into a double wall configuration that is more resistant to destruction. Once past the epithelium, the trophocytes can then breach Bowman's layer and the stroma, making it difficult for topical amoebicidal medications to penetrate.

Early AK is often misdiagnosed. It begins with a "dirty" looking epithelium and pseudodendritic epitheliopathy characterized by epithelial microcysts and erosions.[39] Late AK can have multiple stromal infiltrates, ring infiltrates, scleritis, anterior synechiae, mature cataract and chorioretinitis.[39]

Parasite: Onchocerca volvulus. According to the World Health Organization, onchocerciasis, or river blindness, affects approximately 17.7 million people, of whom 270,000 are blind and 500,000 have severe visual impairment.[40] Onchocerciasis is endemic to West Africa, certain countries in Latin America and Yemen. Simulium black flies that are infected with *Onchocerca volvulus* release the parasitic larvae when they feed on the blood of humans, livestock and birds. The larvae become adult worms, and the females release approximately 1,000 microfilariae each day over a two-week period.[41] The exact pathophysiology of how the microfilariae migrate from the skin and penetrate the conjunctiva is not known; from the conjunctiva, they migrate to the cornea.[42] It is not the parasite but its death and the release of its own antigens that initiates the inflammatory response.

Onchocerca volvulus affects the posterior part of the eye as atrophy of the retinal pigmented epithelium. In anterior disease, motile worms can be seen by slit lamp biomicroscopy in the cornea or anterior chamber. When the parasites die, the inflammatory response is initiated causing epithelial punctate keratitis. With continual exposure to the parasite, the inflammatory response results in opacities as it moves posteriorly to the stroma, ultimately resulting in sclerosing keratitis with irreversible blindness.[43]

Fungi. Since fungi do not inherently penetrate a healthy corneal epithelium, fungal keratitis generally occurs after corneal epithelial trauma from vegetative matter. *Fusarium*, a filamentous septated fungus, is the most common cause of CL-related fungal keratitis, followed by *Aspergillus* and *Candida*.[44] The fungus secretes toxins and enzymes, including serine proteases and matrix metalloproteinases, to invade and colonize the cornea. The motile trophozoite can also encyst rapidly into a double-walled configuration, making it highly resistant to destruction. Associated corneal inflammatory reactions from polymorphonuclear leukocytes cause further damage to corneal tissue.[45] These infections are hard to eradicate as they penetrate deeper into the cornea where there is less exposure to topical antifungal medications. Clinically, fungal keratitis appears as an ulcer with elevated firm hyphae lines that extend beyond the edge of the central ulcer and feathery stromal lesions. Fungal keratitis represents 1% to 39% of corneal infections in the US.[46]

Oomycete-Pythium insidiosum (PI). *Pythium* keratitis is a vision-threatening ocular disease caused by PI, an aquatic oomycete found in tropical and subtropical climates, especially in India and Thailand. Clinically, morphologically and histopathologically, PI keratitis presents very similarly to fungal keratitis. Direct exposure of the cornea to its infectious zoospores from contaminated water or plant material can result in the disease.[47] The zoospores encyst on wounded corneal epithelium and secrete glycoproteins that facilitate surface adhesion. The host's warm body temperature further acts as a stimulus for these zoospores to grow hyphae, which extends on the infected tissue ulcerating the epithelium and penetrates deeper into the cornea.

Clinically, PI keratitis lacks the significant purulence associated with bacterial keratitis. It can present with different patterns of infiltration, the most common having a full thickness stromal infiltrate in the center of the cornea with tentacle-like feathery reticular infiltrates in the subepithelial layer or the anterior stroma.

DYSTROPHIES

The latest International Committee for Classification of Corneal Dystrophies classification of corneal dystrophies identified dystrophies that (1) affect the epithelium and subepithelium, (2) are epithelial-stromal transforming growth factor beta-induced, (3) are stromal and (4) include endothelial dystrophies.[48] Those that affect the epithelium commonly have epithelial defects, which cause associated corneal pain, epiphora and hyperemia. Symptoms range from mild to severe, requiring medical or surgical intervention, and generally tend to recur.

EBMD. Also known as map-dot-fingerprint dystrophy, anterior basement membrane dystrophy and Cogan's microcystic corneal dystrophy, EBMD is the most common of the corneal dystrophies and one of the most likely causes of RCE. It affects between 2% and 43% of the population, though the exact percentage is not known since many patients are asymptomatic. It

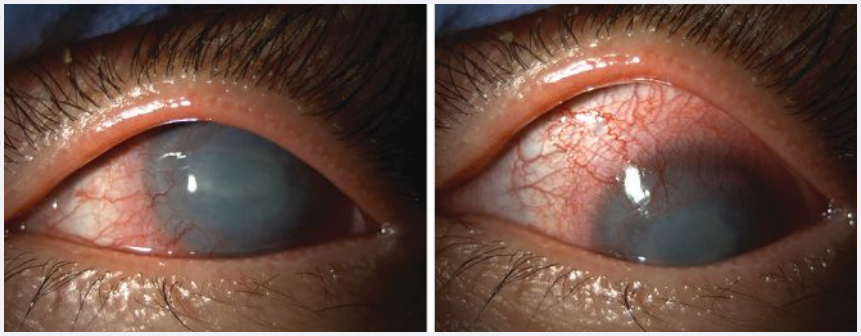

Photo: Suzanne Sherman, OD

AK and conjunctival injection.

generally develops between the ages of 20 and 50 and occurs more in females than males. EBMD is a degenerative condition with, in rare cases, an autosomal dominant mode of inheritance.[49] It generally occurs bilaterally but can be unilateral or asymmetrical in presentation.

In EBMD, the basal epithelial cells are dysfunctional, and this results in the formation of an abnormal epithelial basement membrane. There is also an accumulation of fibrillogranular material between the basement membrane and Bowman's layer and within the epithelium itself.[50] The epithelial basement membrane is thicker, multilaminar and protrudes into the epithelium.[51]

The "map" of map-dot-fingerprint dystrophy is the affected epithelium appearing as large, slightly gray outlines as viewed through the slit lamp. The "dots" are epithelial cells that normally migrate to the corneal surface but get trapped beneath a defective basement membrane that had protruded into the epithelium. Less regularly, the irregular basement membrane forms "fingerprints" of concentric lines in the central cornea. Epithelial cells anterior to the defective basement membrane have difficulty making healthy hemidesmosomes and basement membrane complexes that normally attach to the underlying stroma. This results in RCEs.

Of note, 10% to 33% of EBMD patients have RCEs while 50% of patients with RCEs have EBMD.[5,52] Symptoms of EBMD can range from asymptomatic to debilitating and fluctuate with corneal involvement. They include fluctuating vision, glare, distortion, photophobia and foreign body sensation.[53]

Epithelial recurrent erosion dystrophy (ERED). This includes several distinct dystrophies including Franceschetti corneal dystrophy, Dystrophia Helsinglandica and Dystrophia Smolandiensis. They are rare autosomal dominant conditions characterized by small gray anterior stromal flecks and 0.2mm to 1.5mm diameter whitish-gray, disc-shaped, circular or wreath-like lesions with central clarity in Bowman's layer and the immediate subjacent anterior stroma.[54]

Patients with ERED have frequent painful RCEs caused by impaired epithelial adherence. It generally occurs in the first decade of life but decreases in frequency and severity by 30 to 40 years of age.[55] The frequency and severity of the erosions may cause severe subepithelial scarring and fibrosis resulting in irregular corneas. Given the rarity and unfamiliarity with ERED, the majority of affected patients are either misdiagnosed or not given a specific diagnosis.

Subepithelial mucinous corneal dystrophy (SMCD). This is a rare autosomal dominant epithelial corneal dystrophy currently identified in one single family. Bilateral subepithelial nodular opacities and corneal haze affect the entire cornea but are more dense centrally. These are accompanied by RCEs. It appears during the first decade of life, and vision may decrease after the fifth decade of life. Clinically, it resembles Grayson-Wilbrandt dystrophy but differs histochemically.[56]

Meesmann corneal dystrophy (MECD). Also known as juvenile epithelial dystrophy, MECD is a rare autosomal dominant corneal epithelial dystrophy characterized by small, round microcysts diffusely distributed at different levels in the epithelium. The epithelium may be thickened and disorganized. Microcysts develop during childhood, but MECD often remains asymptomatic until after the age of 40 with the occurrence of corneal erosions, photophobia, excessive lacrimation and decreased visual acuity through the irregular cornea.[57]

CLINICAL PEARLS

Maintaining corneal epithelium health is vital, and it is our job as eyecare professionals to educate patients on how to keep their eyes healthy. When compromised, the epithelium exposes the rest of the eye to a wide variety of insults that can be sight-threatening. Early diagnosis, detailed clinical history, excellent slit lamp biomicroscopy skills and a breadth of treatment options can considerably affect a patient's vision and quality of life. RCCL

Bacterial Strains That Can Cause Keratitis

Bacterial Type	Bacterial Species
Gram-positive cocci	• *Staphylococcus aureus** • *Staphylococcus epidermidis** • *Streptococcus pneumoniae**
Gram-positive bacilli	• *Corynebacterium diphtheriae*** • *Corynebacterium xerosis* • *Listeria monocytogenes***
Gram-negative bacilli	• *Pseudomonas aeruginosa** • *Acinetobacter* species
Enterobacteriaceae species	• *Escherichia coli** • *Klebsiella** • *Serratia** • *Proteus mirabilis**
Gram-negative diplococci	• *Neisseria gonorrhoeae*** • *Neisseria meningitidis*
Gram-negative diplobacillus	• *Moraxella lacunata*
Non-tuberculous mycobacterium	• *Mycobacterium fortuitum* • *Mycobacterium chelonae*
Gram-negative coccobacillus	• *Haemophilus influenza* • *Hemophilus aegyptius***
Gram-positive filamentous	• *Nocardia asteroids* • *Nocardia brasiliensis*

*Most common bacterial causes of keratitis
**Bacterial species that can penetrate an intact cornea

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1. Epithelial apical cells _____.
a. Reside below the wing cells.
b. Have gap junctions that allow molecules to be exchanged directly between individual cells.
c. Have microplicae and microvilli that extend into the tear layer.
d. Multiply by mitosis.

2. RCEs _____.
a. Typically occur in the evenings.
b. Are primarily bilateral.
c. Can cause EBMD.
d. Have weakened or dysfunctional hemi-desmosome attachments.

3. Which organism can penetrate through an intact corneal epithelium?
a. *Corynebacterium diphtheriae*.
b. *Klebsiella*.
c. *Staphylococcus aureus*.
d. *Fusarium*.

4. The most common causes of CL-related keratitis are which of the following?
a. *Acanthamoeba* and *Pseudomonas* followed by *Staphylococcus*.
b. *Pseudomonas* and *Staphylococcus* followed by *Acanthamoeba*.
c. *Acanthamoeba* and *Staphylococcus* followed by *Neisseria meningitides*.
d. *Neisseria meningitides* and *Pseudomonas* followed by *Acanthamoeba*.

5. Inflammation in chronic dry eyes _____.
a. May cause the density of the epithelial layers to decrease.
b. Is the result of tear hypoosmolarity that triggers protease-mediated lysis of tight junctions.
c. Is primarily caused by prolonged CL wear.
d. Can cause desensitization of epithelial nociceptors.

6. Thygeson's SPK _____.
a. Is characterized by one to 50 multiple intraepithelial, elevated corneal epithelial lesions.
b. Is characterized by lesions in the periphery of the cornea.
c. Is a unilateral condition that is caused by viral origins.
d. Can cause blindness.

7. Which of the following is true about ocular allergies?
a. Ocular allergies in combination with dry eyes have a lower allergic response.
b. Approximately 70% of patients with allergic conjunctivitis have corneal involvement.
c. Patients with ocular allergies have an abnormal expression of epithelial junctional proteins.
d. Allergic conjunctivitis affects about 70% of the US population.

8. In neurotrophic keratitis _____.
a. Cranial nerve VI is damaged.
b. Patients have increased corneal nerve sensitivity.
c. The nerves can be damaged from herpes keratitis, head injury and refractive surgery.
d. There is a decreased rate of RCEs.

9. Which of the following is true about herpes keratitis?
a. Herpes simplex and VZV cannot reside in the same ganglion.
b. Varicella zoster causes keratitis during the primary infection.
c. HSV1 is transmitted to the eye through infected venereal secretions.
d. HSV resides latent in the ophthalmic branch of the trigeminal ganglion.

10. Which of the following is not true about EKC?
a. It spreads through contaminated devices like Goldmann applanation tonometry.
b. It is highly contagious and causes ocular keratitis.
c. It presents with punctate or large, geographic-shaped epithelial erosions.
d. Only 10% causes stromal keratitis.

11. Which of the following is not true of bacterial keratitis?
a. The majority of bacterial keratitis arise from *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*.
b. *Pseudomonas aeruginosa* can penetrate the cornea in 72 hours.
c. The ocular pathogenicity of different types of bacteria is related to their ability to adhere to and invade corneal epithelial cells.
d. *Staphylococcus aureus* ocular keratitis has a "ground glass" appearance.

12. Which of the following statements is false?
a. *Staphylococcus aureus* ocular infections present with hyperpurulent conjuntivitis, chemosis and a rapidly progressive stromal infiltration.
b. *Klebsiella* keratitis has whitish-gray pleomorphic suppuration with a diffuse stromal haze.
c. Gram-negative bacteria cause diffuse, quickly spreading necrotic lesions.
d. Gram-positive bacteria tend to produce small distinct abscess lesions.

13. AK _____.
a. Only affects CL wearers.
b. Is often misdiagnosed in its early stages.
c. Is easily treated by amoebicidal medications.
d. Can appear as an ulcer with elevated firm hyphate lines that extend beyond the edge of the central ulcer and feathery stromal lesions.

14. *Onchocerca volvulus* _____.
a. Releases zoospores that encyst on wounded corneal epithelium and secrete glycoproteins that facilitate adhesion to the epithelial surface.
b. Secretes toxins and enzymes including serine proteases and matrix metalloproteinases to invade and colonize the cornea.
c. Infects blackflies whose female worms release approximately 1,000 microfilariae each day over a two-week period.
d. Only affects the epithelium and does not penetrate past Bowman's membrane.

15. Which statement is not true about fungal keratitis?
a. Fungi penetrate healthy, intact corneal epithelium.
b. Motile trophozoite can encyst rapidly into a double-walled configuration that is highly resistant to destruction.
c. *Fusarium*, a filamentous septated fungus, is the most common cause of CL-related fungal keratitis.
d. Fungal keratitis represents approximately 5% to 10% of corneal infection in the United States.

16. Which statement is false about *Pythium* keratitis?
a. PI is an aquatic oomycete found in tropical and subtropical climates.
b. *Pythium* keratitis presents clinically similarly to fungal keratitis.
c. The zoospores encyst on wounded corneal epithelium and secrete glycoproteins which facilitate adhesion to the surface.
d. PI keratitis has significantly more purulence than bacterial keratitis.

17. Which of the following statements is false about EBMD?
a. The apical cells are dysfunctional, and this results in the formation of an abnormal epithelial basement membrane.
b. About 10% to 33% of EBMD patients have RCEs while 50% of patients with RCEs have EBMD.
c. The "map" of "map-dot-fingerprint" is the affected epithelium appearing as large, slightly gray outlines as viewed through the slit lamp.
d. Less regularly, the irregular basement membrane forms "fingerprints" of concentric lines in the central cornea.

18. ERED _____.
a. Includes Franceschetti corneal dystrophy, Dystrophia Helsinglandica and Dystrophia Smolandiensis.
b. Generally occurs in the first decade of life but increases in frequency and severity by 30 to 40 years of age.
c. Is a rare autosomal recessive condition characterized by small gray anterior stromal flecks.
d. Rarely causes RCEs due to impaired epithelial adherence.

19. SMCD _____.
a. Is a rare autosomal recessive epithelial corneal dystrophy.
b. Histochemically resembles Grayson-Wilbrandt dystrophy but differs from it clinically.
c. Appears during the third decade of life.
d. Has bilateral subepithelial nodular opacities and corneal haze affecting the entire cornea that is more dense centrally.

20. MECD _____.
a. Presents with corneal erosions, photophobia, excessive lacrimination and decreased visual acuity.
b. Has symptomatic microcysts that develop during childhood.
c. Is a rare autosomal recessive corneal epithelial dystrophy.
d. Is characterized by small, round microcysts diffusely distributed in Bowman's membrane.

Examination Answer Sheet

The Epithelium in Distress: From RCE to Dystrophy

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1. Ⓐ Ⓑ Ⓒ Ⓓ
2. Ⓐ Ⓑ Ⓒ Ⓓ
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18. Ⓐ Ⓑ Ⓒ Ⓓ
19. Ⓐ Ⓑ Ⓒ Ⓓ
20. Ⓐ Ⓑ Ⓒ Ⓓ

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

21. Recognize the pathophysiology of this structure. ① ② ③ ④ ⑤
22. Describe a healthy epithelium and how it functions. ① ② ③ ④ ⑤
23. Discuss the various conditions that can impact the epithelium. ① ② ③ ④ ⑤
24. Identify when a patient's epithelium is in distress. ① ② ③ ④ ⑤
25. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one)
    Ⓐ 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.
26. 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): ☐
27. 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 for referral ⓔ Change in non-pharmaceutical therapy ⓕ Change in differential diagnosis
    ⓖ Change in diagnostic testing ⓗ Other, please specify: _____
28. How confident are you that you will be able to make your intended changes?
    ⓐ Very confident ⓑ Somewhat confident ⓒ Unsure ⓓ Not confident
29. 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: _____
30. Additional comments on this course: _____

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Rate the quality of the material provided:
1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree

31. The content was evidence-based. ① ② ③ ④ ⑤
32. The content was balanced and free of bias. ① ② ③ ④ ⑤
33. The presentation was clear and effective. ① ② ③ ④ ⑤

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

Signature _____ Date _____

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Corneal Stromal Abnormalities:

Haze, Ectasia, Keratitis and More

A systematic approach to recognizing these threats to health and function is indispensable.

By Susan Gromacki, OD, MS

The cornea's structure is critical to its abilities to refract light and prevent infection. However, it is often susceptible to many menacing threats. The stroma is the thickest layer of the cornea and plays a pivotal role in its stability. This article will present a review of the physiologic and biochemical bases for conditions affecting the corneal stroma that we often see in practice.

AN IMPORTANT LAYER

The cornea is a clear, avascular tissue that covers about one-sixth of the circumference of the globe. It is responsible for two-thirds of the refraction of the eye. Its central thickness is, on average, 535µm, with the periphery being about 100µm thicker.[1,2,3]

The layers of the cornea are, from outermost to innermost: epithelium; anterior limiting lamina (Bowman's membrane); stroma; posterior limiting lamina (Descemet's membrane); and endothelium. The corneal stroma is a mesenchymal tissue, derived from mesoderm. At just over 500µm, it is the thickest layer of the cornea. In its periphery, it is continuous with the sclera.

It is a dense, very regular, connective tissue consisting of flattened, primarily type I collagen fibrils bundled together as lamellae 1µm to 2µm thick that are parallel to the corneal surface, creating the tissue's transparency (*Figure 1*).[4] There are approximately 242 lamellae in the human cornea.[5] They are thinner and more interwoven in the anterior stroma and, as such, there are more of them there than in the posterior stroma. As a result, the anterior stroma is more rigid than the posterior. This plays an important role in corneal curvature and stability.[6] It may also describe why one of the first signs of stromal edema—vertical striae—is always seen in the posterior stroma.[1]

One study demonstrated *in vitro* that the anterior stroma, 100µm to 120µm below Bowman's layer, does not swell perceptibly when the cornea is immersed in water or saline for prolonged periods of time; this swelling takes place only in the posterior stroma, despite the fact that there exist negatively charged proteoglycans in both depths of the stroma.[6]

Keratocytes (fibroblasts) are the primary cells of the corneal stroma.[7] In addition, neutrophils, lymphocytes, plasma cells, and/or histocytes may also be present in very small amounts.[8] They are flat with various long processes extenuating from a central cell body in all directions.[9] Located between the lamellae, they secrete an extracellular matrix (including collagen and proteoglycans) and produce crystalline proteins to help maintain the corneal transparency. The former can also assist in wound healing. Their other functions include assisting in stromal matrix turnover; interlamellar tethering (also helping to maintain transparency); intracorneal communication; and as a reservoir for glycogen (an energy source).[1] There is also a ground substance composed of glycosaminoglycans (GAGs) and glycoproteins. The GAGs are hydrophilic and absorb fluid like a gel.[10,11]

ABOUT THE AUTHOR

Dr. Gromacki is a fellow of the American Academy of Optometry and a diplomate in the Cornea, Contact Lens and Refractive Technologies section. She serves as the director of the contact lens service at a subspecialty group practice in Maryland. In the past year, she has received consulting fees from Alcon, Avellino, Bausch + Lomb SVP, Glaukos, Johnson & Johnson Vision Care, Lentechs, Pentavision, RVL Pharmaceuticals, Santen and Tarsus; and speaking fees from Alcon, Bausch + Lomb SVP, CooperVision SEC, GPLI, Glaukos, PSS Eyecare, Santen and Johnson & Johnson Vision Care.

Fig. 1. The lamellar organization of the corneal stroma allows for its transparency.

KERATOCONUS

This noninflammatory corneal thinning disorder is characterized by a conical protrusion of the central or paracentral cornea. It is usually bilateral, and the thinning is most marked at the apex of the cone.[3,12,13] While there is genetic predisposition, the exact etiology of keratoconus is an enigma, and it is difficult to diagnose in its earliest stages.[13-15] It can be one of the most challenging conditions for eye-care providers to treat, as glasses and traditional soft contact lenses do not provide much benefit. Gas permeable (GP) contact lenses are the mainstay of treatment, and 10% to 25% of these patients will eventually require corneal transplantation, although this number is decreasing with the advent of scleral contact lenses and corneal collagen crosslinking (CXL).[13,16-19]

One author examined the keratoconic cornea histologically and wrote, "Corneal ectasia, a forward protrusion of the tissue, cannot be explained by simple loss of thickness [...] other factors such as lamellar integrity are involved. In keratoconus, ectasia may occur in corneas which are within the normal thickness range [...] thinning appears not to be the only contributing factor for this process [...] (it) also involves biomechanical factors."[1]

A sign of keratoconus—and a primary reason for vision loss and corneal transplantation—is stromal scarring. Another study found stromal scars in 24% of keratoconus eyes. They reported that the scars were always associated with compaction of stromal fibers and suggested that "stromal scarring may be the end-stage of the disarrangement of the stromal structure."[20]

CORNEAL CXL AND HAZE

This procedure was FDA-approved in the United States for keratoconus in 2016 (iLink, Glaukos). It stiffens the cornea, minimizing the ectasia that can lead to vision loss. It uses oxygen, a photoenhancer (riboflavin) and ultraviolet light to induce collagen crosslinks (*Figure 2*). It locks the collagen fibrils together, increasing the thickness of the lamellae. Over 20 years of research confirms the benefits of this procedure.[21,22]

However, in the CXL method where the epithelium is removed prior to the procedure, 90% of patients had haze formation in the anterior to mid-stroma.[23] This can resolve quickly, or may remain permanently, which may in rare cases affect visual acuity. This corneal haze appears as a dust-like change in the stroma or as a mid-stromal demarcation line. Its appearance after crosslinking has a different clinical appearance than haze after other procedures. Corneal haze after CXL was greatest at one month, plateaued at three months, and typically resolved by 12 months. The authors found that corneal haze is not correlated with loss of visual acuity.[23]

CORNEAL TRANSPLANTATION

Over 10% of keratoconus patients will require corneal transplantation to remove the ectatic and scarred stroma.[16,17] Historically, a full-thickness penetrating keratoplasty was performed. However, it was determined that by leaving the endothelium and Descemet's membrane intact, the risk of allograft rejection diminished greatly. Years ago, performing a deep anterior lamellar keratoplasty produced inferior visual results; it also had more intra- and postoperative complications. However, with increased experience over the past decade, this has become the procedure of choice for many surgeons.[24]

Interestingly, the parallel alignment of the posterior lamellae of the stroma facilitates dissection in lamellar corneal grafting. This procedure is, however, not resistance-free, suggesting that there are elements which bind the collagen lamellae together. This is likely due to attachments between the collagen fibrils or the presence of other

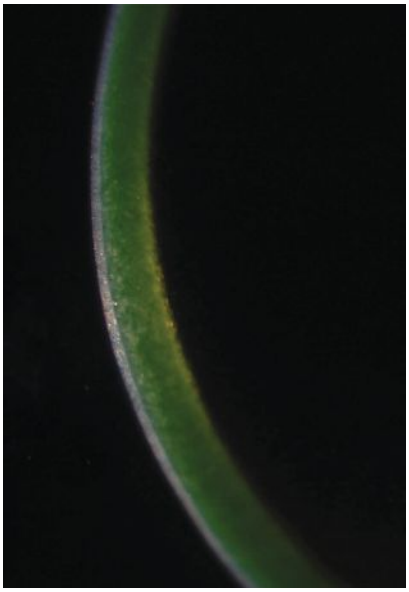

Photo: Roy Rubinfeld, MD

Fig. 2. The green glow of riboflavin indicates adequate penetration into the corneal stroma prior to CXL.

matrix proteins such as the proteoglycans or keratoepithelin.[25]

Patients who have undergone corneal transplantation (including those who have undergone endothelial transplantation) need to be monitored for graft rejection. Signs typically include stromal edema, new keratic precipitates on the endothelium, anterior corneal infiltrates and anterior chamber inflammation. Subepithelial infiltrates, epithelial line, conjunctival hyperemia or neovascularization may also be present. Treatment includes 1% prednisolone acetate q1h, with follow-up every three days. If the edema clears within one week, then diagnose rejection and keep the patient on a steroid dose greater than they were on prior to the episode. If the edema does not resolve, then diagnose corneal failure and refer for a regraft.[26,27]

STROMAL CORNEAL DYSTROPHIES

A corneal dystrophy is bilateral, symmetric, centrally located, avascular and hereditary (typically autosomal dominant and usually unrelated to systemic disease). The newest classification of the corneal dystrophies comes from the International Committee for Classification of Corneal Dystrophies, as described in *Cornea* in 2015.[28] They are divided into categories based on the layer(s) of the cornea that are involved: (1) epithelial and subepithelial, (2) epithelial-stromal transforming growth factor beta-induced, (3) stromal and (4) endothelial

Some of the more common corneal dystrophies involve the stroma:

Granular dystrophy, type 1 *(Figure 3)*:

- White opacities in superficial stroma of central cornea
- 7th-8th decade: opacities enlarge, coalesce and deepen
- Hyaline
- Good visual since the stroma between the lesions remains clear

Lattice dystrophy:

- Refractile lines, anterior-to-mid-stromal dots and faint central haze, subepithelial round opacities
- Stroma between the lesions remains clear until later in life
- Amyloid

Granular dystrophy, type 2 (formerly Avellino dystrophy):

- Granular (early onset) and lattice (later) changes in same eye
- Hyaline and amyloid

Macular dystrophy:

- Diffuse, grayish-white spots in central portion of anterior stroma → 3rd decade: extends to endothelium and limbus→ Descemet membrane opacified and endothelial guttata
- Mucopolysaccaride

Schnyder (crystalline) dystrophy:

- Round, oval, discoid or annular central opacity composed of needle-shaped crystals, sometimes with arcus and limbal girdle
- Cholesterol

Fleck dystrophy:

- Small, discrete, dandruff-like specs in the stroma that extend to the periphery
- Visual acuity good

The stromal lesions may induce irregular astigmatism. Initially, GP (corneal or scleral) lenses may correct the irregular astigmatism created by the lesions. If the dystrophy worsens—and it is anterior enough in the stroma—phototherapeutic keratectomy may be performed to ablate the deposits. Later, if the deposits create even more serious vision loss, a corneal transplant may be performed.[29]

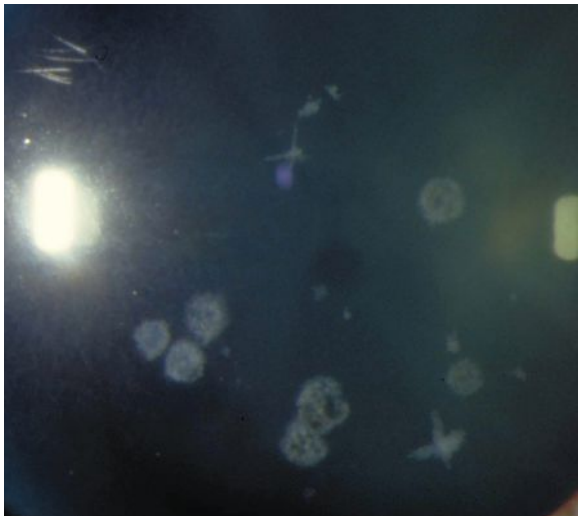

Fig. 3. Granular dystrophy in a 39-year-old woman.

STROMAL EDEMA

If the epithelial or endothelial barrier is damaged, or the endothelial pump compromised, there will be an uptake of water into the stroma, resulting in swelling. The loss of the endothelial barrier results in a much greater corneal thickness increase than the loss of the epithelial barrier. The corneal stroma swells due to the hypertonic nature of the collagen, salts and proteoglycans. With corneal edema also comes a loss of proteoglycans.[11]

Histologically, in a swollen cornea the collagen fibrils are no longer of equal distance from each other. This causes a loss of transparency.[11]

Contact lens wear. The avascular cornea typically receives its oxygen from the atmosphere. However, the hypoxia created by lens wear can create stromal edema. Central corneal clouding could occur after just a few hours of wearing the lenses (*Figure 4*). Hallmark studies taught practitioners and material manufacturers alike which materials, lens thicknesses and wearing schedules were necessary to prevent corneal edema.

So, what is the mechanism whereby hypoxia causes stromal swelling? The lack of oxygen causes metabolic changes that can affect the epithelium, limbus, stroma and endothelium. Stromal swelling, in particular, results from increased lactate content following hypoxia.[10]

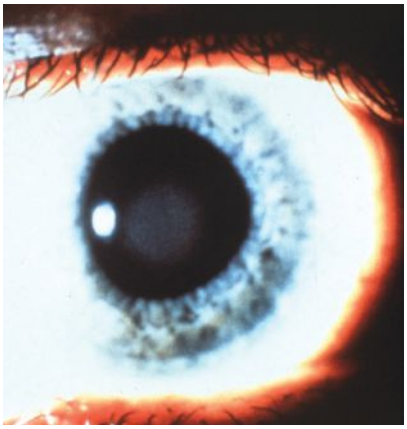

Photo: Lisa Badowski, OD, MS

Fig. 4. Central corneal clouding caused by PMMA lens wear.

Patients often overwear their lenses and sleep in them, creating hypoxic conditions. Failing to clean them properly results in deposits on the lenses that can prevent the passage of oxygen to the cornea. Scleral GP contact lenses are three times the thickness of corneal GP lenses and cover the entire cornea. Corneal GPs allow oxygen to pass around the contact lens to the peripheral cornea. The oxygen needs to pass through the under-lens tear layer, and the thicker the layer the less readily oxygen will pass through. Much research has been conducted on this topic to ensure that these fantastic lenses for correcting corneal irregularity are not causing other problems for our patients. However, some of today's lenses are still too thick, and the tear layers too deep, to prevent corneal edema during lens-wearing hours.[30]

Infectious keratitis (corneal ulcers). This is often categorized as *Acanthamoeba*/parasitic, bacterial, fungal or herpetic. Treatment needs to be quick and aggressive to avoid the corneal scarring that can lead to corneal transplantation.

Aphakic/pseudophakic bullous keratopathy. Corneal edema can occur in eyes after the intraocular lens has been removed. This may be caused by a preferential loss of anterior stromal keratocytes.[25] Additional signs include corneal bullae, Descemet's folds, corneal neovascularization, endothelial guttata, elevated eye pressure and/or cystoid macular edema (CME). Treatment includes topical sodium chloride 5% drops QID and ointment at night. If the bullae rupture, use a bandage contact lens to facilitate healing and use an antibiotic to prevent infection. The elevated eye pressure and/or CME will need to be treated as well.[31]

Other etiologies. Stromal edema can also be found in congenital glaucoma, angle-closure glaucoma, birth trauma (forceps injury), corneal abrasions and other corneal injuries.

TAKEAWAYS

The corneal stroma is a remarkable structure. It is imperative to maintaining corneal clarity and sturdiness. As practitioners, it is important for us to help our patients maintain this transparency so that they can maximize their vision at all times. RCCL

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The Endothelium and Corneal Transparency: A CLEAR CONNECTION

Learn how multiple complications can affect clarity and performance.

By Bhawan Minhas, OD

The endothelium—the posterior facing and thinnest layer of the cornea—is often taken for granted. This simple layer plays a critical role in maintaining transparency of the "window" of the eye, allowing visualization not only of the anterior ocular structures but also the posterior segment. This fragile structure is comprised of a monolayer of six-sided cells, void of replication capabilities and tasked with maintaining structural hydration. Understanding the pathophysiology of abnormal function is vital for clinicians to develop a refined treatment and management plan when faced with a cloudy cornea.

THE NORM

Overall, the barrier to external invaders is maintained by the corneal epithelium; maintenance of thickness and shape for refractive power is provided via the stroma, and hydration and nutrition are the responsibility of the endothelium.[1] Corneal nutrients, save oxygen, are predominantly obtained from the aqueous humor via passive diffusion and active transport on the apical and basolateral flanks of the endothelium.[2,3] The endothelium has a two-part job in its role of maintaining hydration and nutrition with an active "pump" and a passive "leak" component.[4] The resultant hydrostatic pressure of the aqueous and the oncotic pressure of the cornea maintains tissue deturgescence.[5]

Endothelial cell patterns are specifically designed to facilitate their function and often mimic that of "foam-like" material.[6] Endothelial hexagonality falls in line with von Neumann-Mullins law, which indicates that cells with greater than six sides grow and cells with fewer shrink—allowing hexagonal cells to maintain equilibrium.[6] Cell growth in adults demonstrates a classic linear pattern with mean cell size (MCS) increasing proportionally with age and a corresponding decrease in endothelial cell density (ECD).[6] Moreover, there are slightly more smaller cells in the periphery compared with centrally, thought to occur due to finite corneal space.[6]

The classic hexagonality that is visualized when considering corneal endothelial cells (ECs) only holds true for their apical surface, which is in contact with the aqueous humor; the basal surface has been modeled to be irregular in nature.[3] The apical, hexagonal shape is maintained by tight junctions and a sub-membranous network of actomyosin along the lateral borders where the ion pumps reside.[3]

SENESCENCE

Aging affects all parts of the visual system. However, it affects ECs particularly harshly, as they cannot rely on regeneration to maintain function and are subject to apoptosis over their lifetime.[5,7] The average adult holds an ECD of approximately 2,500 to 3,000 cells per mm^2; however, corneal clarity can be maintained at a critical mass of 400 to 700 cells per mm^2 in individuals with average intraocular pressure (IOP).[8]

Due to this natural and ongoing deterioration of EC numbers, the remaining cells often morph via centripetal migration and stretching in order to compensate for lost comrades.[9] In the absence of mitosis

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Dr. Minhas currently serves as the Associate Dean of Accelerated Programs at Pennsylvania College of Optometry (PCO) at Salus University. She oversees the three-year Accelerated Scholars Program and the Advanced Placement Optometry Degree Program in this capacity. She works closely with students in the Traditional and Scholars programs and in the residency program at PCO in clinic, lecture, lab and grand rounds. She has no financial interests to disclose.

in vivo, changes in MCS (polymegethism) and cell shape (pleomorphism) are direct consequences of the reduction in ECD—namely, disruption of the pump-leak process required to maintain tissue transparency.[7,10] There is evidence of this change in uniformity when reviewing the coefficient of variation (CV) of mean cell area—a measure of polymegethism—and the proportion of hexagonal cells—a measure of pleomorphism. With time, the former increases from 0.22 to 0.29 and the latter decreases from 75% to 60%.[11]

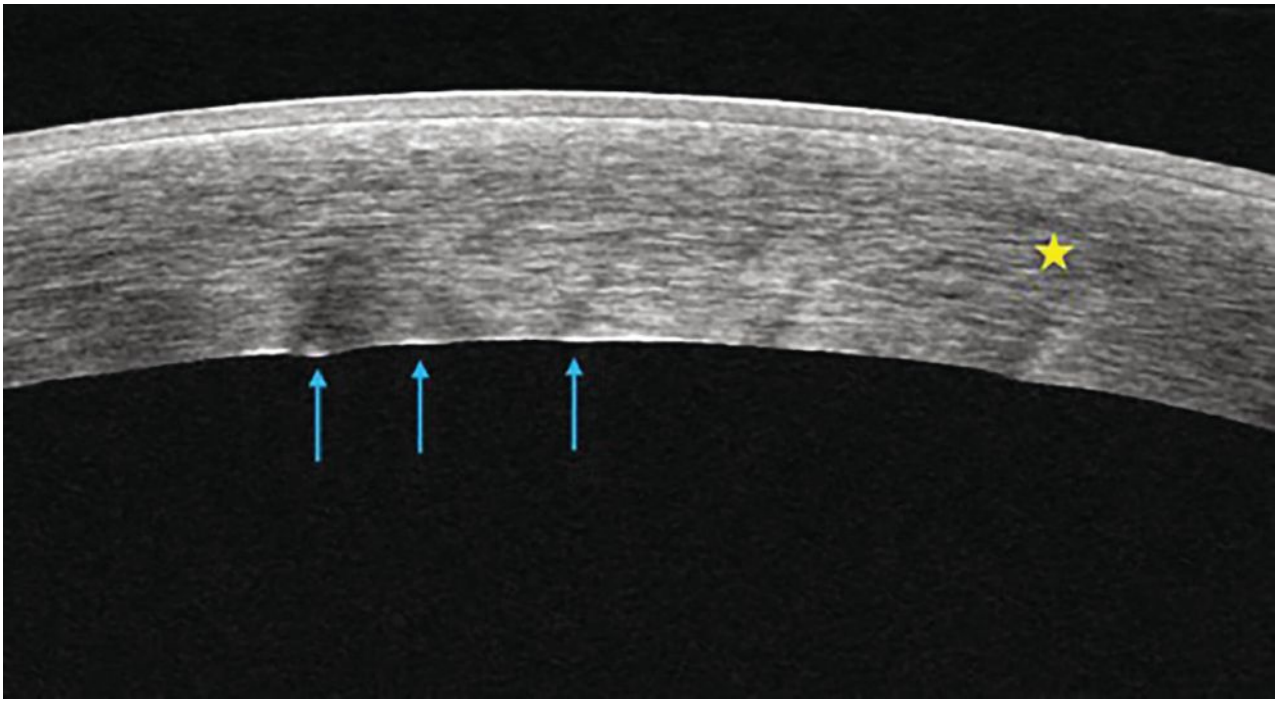
GENETICS

The most commonly encountered endothelial corneal dystrophies include Fuchs' dystrophy, posterior polymorphous dystrophy (PPD) and congenital hereditary endothelial dystrophy (CHED). Though the three conditions have varying genetic bases and modes of inheritance, all lead to a mutation's resulting errors in transcription factors, structural components of the stroma and Descemet's membrane, or cell transport proteins.[12] Regardless of genetic cause, each dystrophy can halt the pump-leak process of the corneal endothelium, leading to edema, increased scattering of light, scarring and loss of vision.

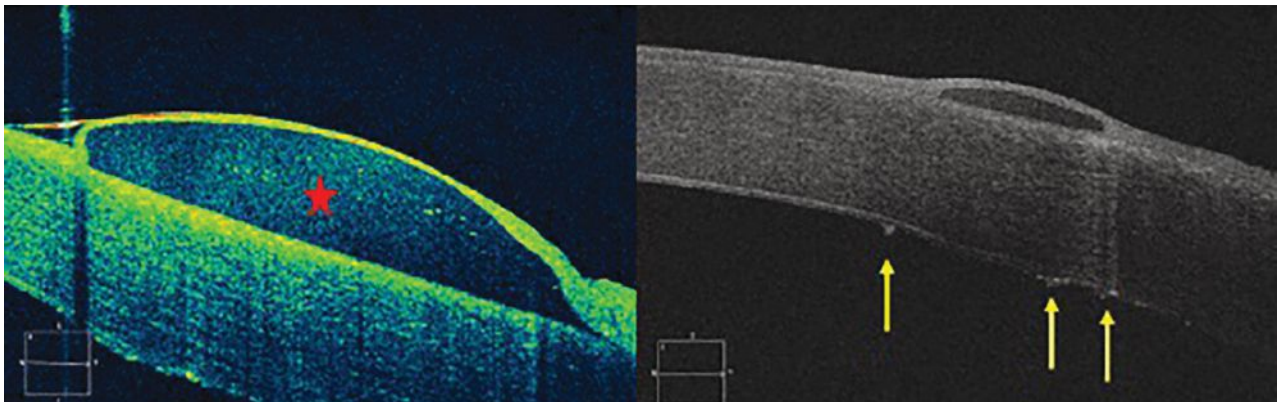
Fuchs' is the most common corneal endothelial dystrophy and includes two distinct genetic variations: early-onset Fuchs' and the more common late-onset Fuchs', both marked by the presence of guttae greatest centrally.[13] Early-onset Fuchs' includes a mutation of the COL8A2 gene thought to have autosomal dominant inheritance and lead to changes in a component of Descemet's membrane.[12,14]

Late-onset Fuchs', however, reveals high genetic heterogeneity and has been associated with several genes, including FECD2 (13pter-q12), FECD3, TCF4, FECD4, SLC4A11, FECD5 (5qdd-35), FECD6, ZEB1, FECD7 (9q24-22), FECD8, AGBL1, FECD, DMPK and TCF4 intronic repeat sequence. This type of Fuchs' displays mixed effects, like disrupted functions for Descemet's membrane, transcription factors, ion transport, glutamate decarboxylase and protein kinase.[12] Areas between guttae demonstrate increased CV and mean cell area.[12] Unlike with senescence, enlarged ECs are noted to secrete excess basement membrane in the form of banded collagen, further exasperating the pump-leak dysfunction.[13]

PPD includes epithelium-like characteristics of the endothelium, but with less severe clinical signs and symptoms. However, there is an increased possibility for extension of the trabecular meshwork and a resultant rise in IOP.[13] Mutations in OVOL2 (PPCD1), ZEB1 (PPCD3) and GRHL1 (PPCD4) and autosomal dominant inheritance are known to be associated with PPD.[12] Unsurprisingly, these genes are key regulators of differentiation, and variance leads to changes



Anterior segment OCT of a cornea with microcystic stromal edema (yellow star) and endothelial folds (blue arrows) secondary to endothelial pump dysfunction from herpetic disease.



Anterior segment OCT of a corneal bullae (red star) in a patient with uncontrolled Fuchs' endothelial dystrophy leading to stromal edema and ultimately bullous keratopathy. Left photo shows initial presentation and right photo is near resolution with large endothelial guttae visible (yellow arrows).

in cell type, either from epithelial to mesenchymal or vice-versa.[12]

CHED, the endothelial dystrophy present from birth, has both a dominant and recessive form and is associated with OVOL2 and SLC4A11, respectively.[12] There is significant stromal haze in both forms and a strong association with childhood glaucoma.[12] The autosomal recessive form presents with a milky cornea in the first few weeks of life, along with diffuse opacity, a ground-glass appearance, increased corneal thickness, lack of ECs and homogenous thickening of Descemet's membrane.[12] Alternately, the autosomal dominant form develops opacity after the first year of life and appears with an absence of an endothelial mosaic.[12]

TRAUMA

The corneal endothelium responds to injury in three stages:

(1) Migration of adjacent ECs to fill the wound

(2) Re-establishment of tight junctions

(3) Remodeling of ECs into a regular hexagonal shape[4]

The initial stage is immediate, and the latter two stages can take up to several months.[4] The corneal endothelium is remarkably resilient to injury—whether that be in the form of trauma or ocular surgery. Its tenacity is due to several factors, including increased peripheral endothelial cell number ready for migration, ability of ECs to form new tight junctions to maintain function, an increase in endothelial Na+/K+ ATPase pump sites under stress, homeostatic concentrate of Na+ in the aqueous humor allowing the osmotic gradient and the ability of ECs to shift their metabolism of glucose to the hexose monophosphate shunt for NADPH and membrane repair.[15]

The impact of various intraocular surgeries on the corneal endothelium and resultant bullous keratopathy have been studied in order to establish best practices, with cataract extraction having the most data. Manual small-incision cataract surgery with posterior chamber intraocular lens implantation has been shown to cause 15.8% endothelial cell loss.[16] With or without intraocular lens implantation, ECD has been demonstrated to continue to decrease at an annual rate of 2.5% for at least 10 years after initial decline.[17]

Post-cataract surgery endothelial cell loss has revealed to be amplified in diabetic patients compared with unaffected individuals.[18] Furthermore, phacoemulsification in the context of a decreased endothelium to iris distance has been associated with increased rate of EC loss.[19] Surgeons often avoid endothelial compromise by remaining cognizant of chamber depth, cataract density, phaco time, surgery time, ultrasound power, intraocular lens contact, instrument-related trauma, incision size, incision location, irrigation solution turbulence, intraocular lens type and viscoelastic substance.[18,20] Additionally, hydrogen in the form of H^2 dissolved in ocular irrigation solution allows protection of ECs from phacoemulsification-induced oxidative stress and damage.[21]

ECD loss is evident in suprachoroidal microinvasive glaucoma surgery (MIGS), Schlemm's canal implantable devices, Schlemm's canal procedures without implantable devices, trabeculectomy and aqueous shunt surgery.[22] Combined glaucoma MIGS involving long-term implants do not show more endothelial decompensation than glaucoma filtration surgeries alone.[22]

There has been evidence of corneal decompensation with laser iridotomy and Nd:YAG laser with proposed mechanisms for direct focal injury, thermal damage, mechanical shock waves, iris pigment dispersion, transient rise in IOP, inflammation, turbulent aqueous flow, time-dependent shear stress on ECs, chronic breakdown of the blood-aqueous

barrier and damage from bubbles that settle on the endothelium.[23] The need for Nd:YAG laser capsulotomy within one year of cataract extraction has been postulated as the mechanism for post-op ECD decline.[24] Endothelial health should also be considered in posterior segment procedures as ECD exhibits a decrease in retinal photocoagulation with an indirect ophthalmoscopy contact lens.[25]

CONTACT LENSES

Hypoxic stress can cause endothelial changes in cell morphology, including polymegethism, pleomorphism and alteration of microanatomy that can be linked to contact lens wear.[13,26,27] Though not as common, hard and soft polymethylmethacrylate lenses were noted to cause the most significant changes in ECD.[27]

There is less evidence that ECD or central corneal thickness is affected by chronic contact lens use of newer materials.[26] Endothelial intercellular pH changes due to hypoxia-induced CO^2 increase, lactate buildup, reduced availability of anterior chamber oxygen and endothelial bleb (small black spots appearing as disruptions on the endothelium) formation may all be culprits of endotheliopathy in contact lens users.[28] What's more, patients with corneal grafts can be at a higher risk for further endothelial compromise, and those fit in specialty contact lenses should be closely monitored.

DISEASE SEQUELAE

Incidence of glaucoma has been linked to changes in ECD due to the suggested mechanism of increased IOP accelerating cell loss.[29] When looking at cell density in patients with pseudoexfoliation post-cataract surgery, those with glaucomatous damage demonstrated a decreased ECD when compared with those with the syndrome.[30]

Carbonic anhydrase has an important function in the pump-leak process of the endothelium, thus carbonic anhydrase inhibitors (CAIs) that can cause pump dysfunction are a natural culprit to consider. Endothelial pump deceleration, acidification of the ECs and interference with intercellular pH regulation have been noted when CAIs are applied directly to ECs *in vitro*.[31] Topical and oral CAIs—such as dorzolamide or brinzolamide—have been anecdotally linked to increased corneal thickness and decreased ECD; however, this has not been proven to be clinically significant in studies on patients with normal baseline ECD.[32,33]

In individuals with pre-existing endothelial dysfunction, the use of dorzolamide has been linked to a 12µm thickness increase.[34] Endothelial toxicity to benzalkonium chloride or other preservatives, rather than the active medication, has been hypothesized to cause breakdown of the apical barrier's functioning, but changes are thought to be dose- and time-dependent.[35,36] Finally, there is some suggestion that topical prostaglandin analogs, beta-blockers, alpha agonists, CAIs and miotics used for glaucoma management may affect physiological endothelial function via changes in Ca^{2+} mobility.[37]

Changes in MCS, cell shape, increased rate of endothelial cell death and corneal edema—similar to that seen in Fuchs'—have all been demonstrated in patients with diabetes mellitus (DM).[38] One study found that there was an 11% reduction in ECD in DM Type 1 vs. a 5% reduction in DM Type 2, while displaying a progressive decline in ECD with disease duration and higher HbA1c.[37,39,40] Evidence for cell mitochondrial swelling, metabolic dysfunction, decreased Na+/K+ ATPase function, poor tight junction formation and changes to the extracellular matrix have been linked as potential causes.[37]

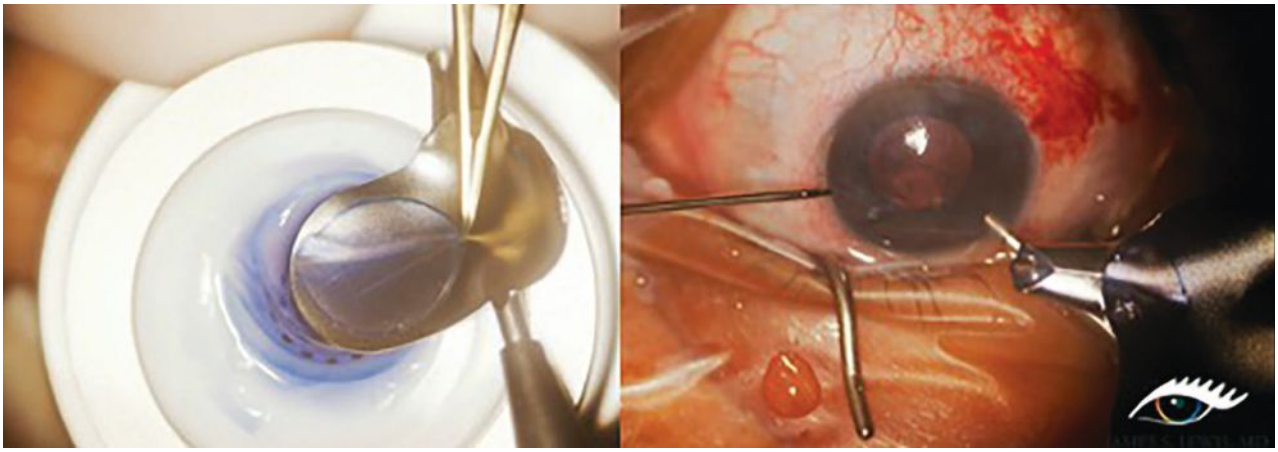


Photo: James Lewis, MD

Left: A 9mm donor graft is loaded in preparation for DSEK procedure in patient with severe endothelial decompromise. Right: Donor tissue is folded up like a taco with endothelium side up in order to insert through a temporal incision.

Though there is confounding literature, most studies suggest that diabetes accelerates endothelial cell dropout and is associated with decreased central ECD and increased CV likely secondary to metabolic changes causing endothelial instability.[41] Even further, chronic kidney disease in patients with or without DM can be linked to vulnerability in decompensation due to polymegethism and pleomorphism.[42]

Secondary inflammation of the endothelium—called endotheliitis—has been connected to viruses of the herpes family. Characteristic findings include keratic precipitates, anterior chamber inflammation, endothelial dysfunction and resultant corneal edema. The inflammation is classified into four discrete types: linear, sectoral, disciform and diffuse.[43] It has been postulated that this is likely an anterior chamber–associated immune deviation disease modulated by viral antigens.[44] This gives credibility to the idea that systemic viral pathogens can cause an inflammatory response in ocular structures; in fact, recent evidence for patients testing positive for COVID-19 suggests that endothelial changes during active infection could help understand the systemic effects of the disease.[45]

TAKEAWAYS

The endothelium warrants further attention than its 5µm thickness initially implies, as it plays a key role in corneal clarity. Considerations go well beyond initial understanding and require continuous re-evaluation. Astute optometrists should evaluate the structure carefully in order to unearth subtle changes that can later lead to deleterious effects. Additionally, linking ocular pathology to systemic considerations is vital in holistic care of our patients. RCCL

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By Rebecca Rojas, OD and Suzanne Sherman, OD

If at First You Don't Succeed...

Learn how to deal with the stubborn condition of recurrent corneal erosions when initial treatment fails.

A 39-year-old male presented with tearing, redness and pain in his right eye. He denied any trauma or previous injury to his eye but did report irritation and dryness about two to three days prior. After a detailed history, he did not report having a similar incident in the past and noted that the foreign body sensation and irritation was not alleviated with use of OTC Visine (tetrahydrozoline, Johnson & Johnson) drops.

Upon examination, a linear abrasion was found inferiorly on the cornea outside the visual axis. The patient was diagnosed with a corneal abrasion and instructed to use antibiotic drops (ofloxacin 0.3%) TID to prevent infection of the open wound and lubricants for any irritation or discomfort. He was asked to follow-up one week or sooner with any worsening of symptoms. He returned in one week with a clear and healed cornea with no epithelial defect noted. He discontinued the antibiotic and was instructed to continue using lubricants as needed.

Two months later he presented with similar symptoms of pain, redness, tearing and areas of negative staining with minor breaks in the epithelium, consistent with epithelial microcysts, in the inferior region of the cornea. He was diagnosed with recurrent corneal erosion; flare-ups continued to occur over several weeks. Treatments included bandage contact lens (BCL) placement, Acuvue Oasys (8.8/14.0) (Johnson & Johnson) with the antibiotic ofloxacin 0.3% QID during the acute phase to prevent infection and again, lubricants throughout the day for comfort. The patient was asked to follow-up in three days. Once the epithelium was healed and the BCL was removed, he was instructed to start Muro 128 5% ointment (Bausch + Lomb) at night and to use Lotemax (loteprednol etabonate, Bausch + Lomb) BID OD.

Recurrences took place over the course of several weeks and months. A longer-term treatment of a BCL was tried with antibiotic ciprofloxacin QID for three weeks with close monitoring and weekly follow-ups. Two weeks later, another recurrence happened. Conservative therapy options proved ineffective and discussion regarding other treatment options, including amniotic membrane placement, superficial keratectomy Diamond burr debridement and phototherapeutic keratectomy, was had, before ultimately deciding on undergoing phototherapeutic keratectomy, which occurred without complications.

After treatment at his one month follow-up, the patient was doing well without any further complications or recurrences.

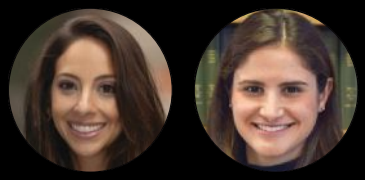
RECURRENT CORNEAL EROSIONS (RCEs)

These are frequently encountered in practice and characterized by basal epithelial cells that do not attach to the basement membrane, resulting in abrasions. Damage to the epithelium or epithelial basement membrane can result from previous instances of trauma or abrasions (*e.g.*, sharp abrasion from a fingernail, tree branches or paper edge cuts), corneal dystrophies and degenerations or prior surgeries where the corneal epithelium has been removed (*i.e.*, corneal transplantation, epi-off crosslinking, cataract surgery and keratorefractive surgery).

In healthy patients, the injuries usually heal quickly if they are superficial enough, leaving the cornea without evidence of damage during clinical examination. Symptoms tend to recur over the course of days but can even persist for years, resulting in chronicity. These include acute ocular pain, foreign body sensation, tearing and photophobia.

Diagnosing an RCE requires a detailed history and careful slit lamp exam. There is often a history of prior abrasion of the involved eye and pain usually occurs immediately upon waking or in the middle of the night. Clinical presentation may not correlate to the exam findings, thus it is important to look for subtle corneal changes, like areas of negative staining that highlight loose epithelial adhesion. Other changes could take the form of epithelial microcysts, visible with retroillumination, areas of sodium fluorescein pooling around the affected area or use of a Weck-Cel spear to confirm areas of loose adhesion. Shahinian's sign (corneal valance) is noted in epithelial basement membrane dystrophy, which is described as a "scalloped line of tear film thinning" seen in the slit lamp with use of NaFl dye and cobalt blue filter.[1]

Episodes can vary in duration and intensity of pain associated with the epithelial defect. Some can last as little as 30 minutes and improve with use of artificial tears, while larger abrasions can leave the patient with intense pain, eyelid edema and decreased vision.



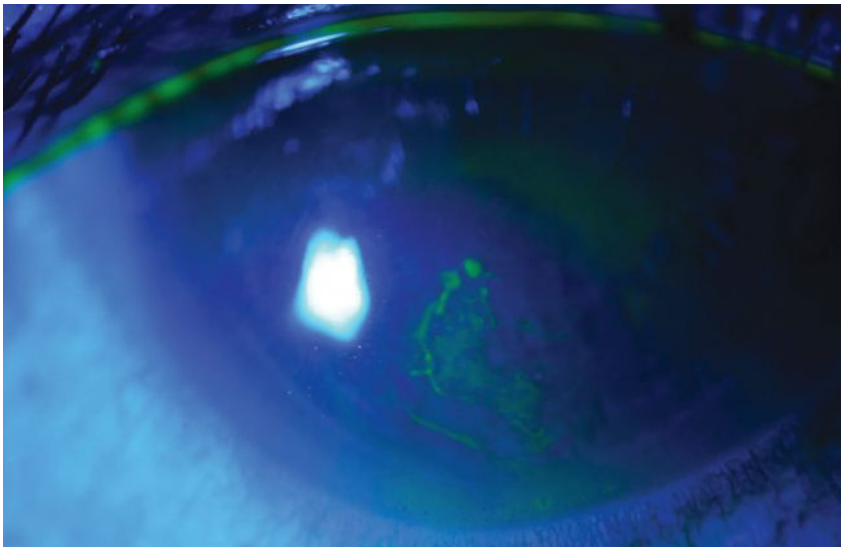


Photo: Rebecca Rojas, OD

A macroform erosion with loosely adherent epithelium is highlighted with NaFl staining.

Differential diagnosis of RCEs include herpes simplex virus, epithelial keratitis, neurotrophic keratitis, exposure keratopathy, infectious corneal ulcers, trauma and scratches, leading to corneal abrasions and ocular graft-versus-host disease.[2]

TOPICAL THERAPEUTICS

Treatment for RCEs varies depending on the severity of the erosion and symptoms experienced. The primary goal is to relieve pain and provide re-epithelialization, while the long-term goal is to prevent recurrences. Conservative treatment includes topical lubricant gel or ointment at night with topical cycloplegics and oral analgesics for pain control. A BCL helps smooth out epithelial areas with corneal irregularities and allows for better cell adherence, while antibiotic drops help reduce the risk of secondary infection. When using BCLs, make sure there is high DK (oxygen transmissibility) and adequate fit and movement of the lens. Long-term use of antibiotics should be monitored carefully and not used for extended periods of time.

Patients with ocular rosacea or meibomian gland dysfunction (MGD) causing chronic dry eye are more at risk for erosions and improper healing because of free fatty acids found in their tear secretions. They may benefit from punctal plug occlusion for either temporary or long-term prophylactic treatment, effectively increasing the lacrimal lake and aiding in dry eye.[1]

Patients with diabetes also suffer from corneal complications impacted by trauma and delayed wound healing, resulting in recurrent erosions to neurotrophic keratopathy. Recovery time varies and should incorporate comanagement with the patient's endocrinologist.[3]

Other forms of treatment include a combination of topical steroids with a dose of oral doxycycline.[4] Increased levels of matrix metalloproteinase (*i.e.*, MMP2 and MMP9) have been found in tears of patients with RCEs. These enzymes cause a separation in the epithelial layer by dissolving the basement membrane and fibrils from hemidesmosomes. Therefore, the use of MMPase inhibitors has been studied as another form of treatment. Doxycycline is an MMP9 inhibitor which, along with corticosteroids, is effective in reducing frequency of RCEs.[5] This combination therapy has been specifically helpful to patients with associated MGD because it helps lower the production of lipase, which affects the healing and quality of epithelial membranes.[4]

Autologous serum tears have been effective by providing lubrication along with essential nutrients and growth factors to help promote epithelial healing, including cytokines, vitamin A, epithelial growth factor, vitamin C and fibronectin.[4,6] Studies have confirmed successful treatment of RCEs for 12 to 24 month periods without recurrences after use of autologous serum tears.[7]

Amniotic membrane placement over debridement of loose epithelial tissue results in epithelialization within four to seven days, as it reduces inflammation and promotes healing.[8] Areas of loose epithelial tissue benefit from mechanical debridement to provide a smooth area for re-adherence. One of the quickest and most effective ways is to debride loose tissue at the slit lamp. This is done with use of one drop of topical proparacaine and ophthalmic instruments or sponges to debride and remove excess debris. Tools used range from Weck-Cel spears, shaped methylcellulose surgical sponges, blunt spatulas and jeweler's forceps.[9]

By Rebecca Rojas, OD and Suzanne Sherman, OD

If at First You Don't Succeed...

(Continued from p. 37)

SURGICAL INTERVENTIONS

When other treatments fail, surgical intervention is warranted. Diamond burr superficial keratectomy is performed on patients who have erosions that are on or near the visual axis, while anterior stromal puncture is considered for erosions outside the visual axis. This is because anterior stromal puncture has been shown to produce glare, scarring and blurred vision, while only providing moderate efficacy in preventing erosions.[9]

Anterior stromal puncture can be performed using a needle or laser providing injury to Bowman's membrane that results in better adherence to epithelium.[9] Diamond burr superficial keratectomy has a higher success rate than anterior stromal puncture, with the advantage of avoiding the use of lasers or sophisticated equipment. Other advantages of superficial keratectomy include decreased risk of corneal perforation, scarring or refractive changes and less recurrences than epithelial debridement alone.[10]

Phototherapeutic keratectomy (PTK) is used on patients who suffer from micro- or macroerosions secondary to ocular trauma when conventional therapy has failed. PTK can also treat areas near the visual axis; however, inducing refractive changes may be more likely to occur than in other treatment modalities, especially with the use of older lasers or deeper ablation.[11] Despite this possibility, all surgical interventions are performed with a high success rate because it allows the epithelium to heal and re-epithelialize by adhering to the basement membrane with a stronger bond, preventing recurrences.

NON-SURGICAL INTERVENTION

A newer modality cited in literature is use of scleral contact lenses for RCEs or persistent epithelial defects. These therapeutic lenses are effective in promoting the healing of defects that have failed with topical or surgical intervention. The healing response is attributed to oxygenation of the corneal epithelium and protection of the epithelium during recovery.[12]

Corneal erosions can be debilitating for the patient when they have recurrent episodes with pain that interrupts their ability to sleep or continue with their daily activities. There are several treatment options available to alleviate discomfort in the acute phase, but patient education is important to impart the necessity of compliance in determining the treatment modality for chronic cases. Advances in treatment have provided relief in reducing recurrences and allowing patients the ability to return to their normal lives. As clinicians, it is vital to closely monitor these patients and provide the proper referral for advanced surgical intervention when necessary. RCCL

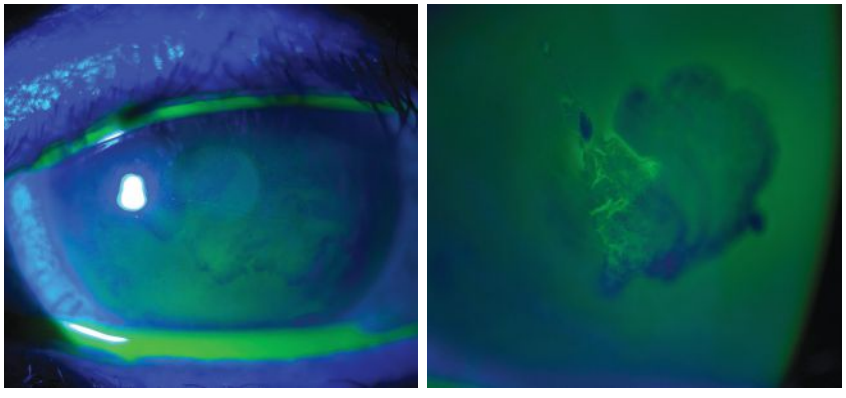


Photo: Suzanne Sherman, OD

An erosion that is healing after a successful use of a Prokera graft.

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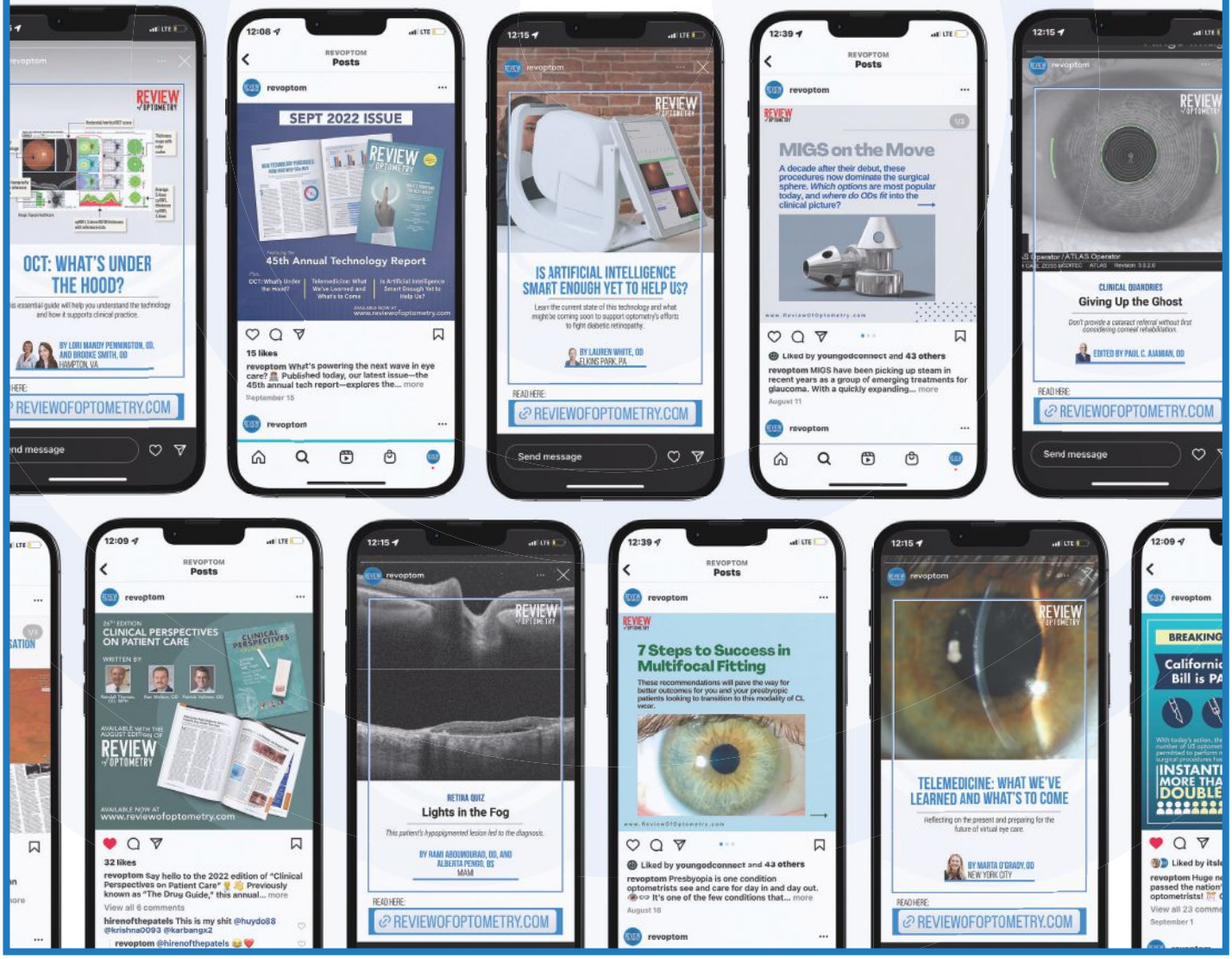

By Christine W. Sindt, OD

Having a Meltdown

Peripheral ulcerative keratitis has potentially devastating consequences. Treatment requires aggressive systemic control combined with interventions to protect the ocular surface.

A 67-year-old male presents with complaints of bilateral ocular pain and photophobia, increasing in severity over the past week. He says the pain is an 8/10 and nothing relieves the discomfort, and he prefers a dark room with his eyes shut. His medical history is only significant for hepatitis C.

On ocular examination, deep guttering and staining is seen adjacent to the limbus nasally OD and temporally OS, both spanning six clock hours, with areas of exceedingly thin stroma at risk for perforation. He was diagnosed with peripheral ulcerative keratitis (PUK) and started on moxifloxacin TID OU, vitamin C 2000mg daily, doxycycline 100mg BID and ibuprofen 800mg TID. He was also fit with a scleral lens and referred to rheumatology for systemic evaluation.

CAUSES AND INTERVENTIONS

PUK is associated with autoimmune diseases such as Sjögren's syndrome, granulomatosis with polyangiitis, relapsing polychondritis, systemic lupus erythematosus, polyarteritis nodosa and most commonly with rheumatoid arthritis. Differential diagnoses includes Mooren's ulcer and Terrien's marginal degeneration. PUK (also known as corneal melt) develops when there is an imbalance between specific collagenase (MMP-1) levels and tissue inhibitors (TIMP-1). This imbalance can cause keratin in the corneal epithelium to break down rapidly. As the stroma thins, the eye is at risk for corneal perforation, which can lead to vision loss.

In addition to topical antimicrobials, oral doxycycline is used for its anti-collagenase activity, along with oral vitamin C to promote collagen synthesis and stromal repair. Topical corticosteroids should be avoided because of the risk of accelerating keratolysis and suppressed wound healing. Topical 1% medroxyprogesterone acetate (compounded drop) may be helpful

Photo courtesy of Sara Downes, OD

Having a Meltdown

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in cases of PUK because it reduces inflammation and promotes collagen repair. Scleral lenses are helpful by keeping the ocular surface moist and preventing exposure-related breakdowns of the epithelium. In addition, scleral lenses improve ocular comfort and decrease inflammation.

Systemic immunosuppression is often required to control ocular inflammation. Initial treatment is with oral steroids, prednisone (1mg/kg/day) or methylprednisolone (1g/day x 3 days). In cases with impending perforation not controlled by steroids, or in patients with rheumatoid arthritis who are at risk for vascular events, steroid-sparing agents are used. These include antimetabolites such as methotrexate, azathioprine or mycophenolate mofetil, T-cell inhibitors such as cyclosporine or tacrolimus, alkylating agents such as cyclophosphamide and chlorambucil, and biologic agents such as infliximab and rituximab.

MANAGEMENT COURSE AND PROGNOSIS

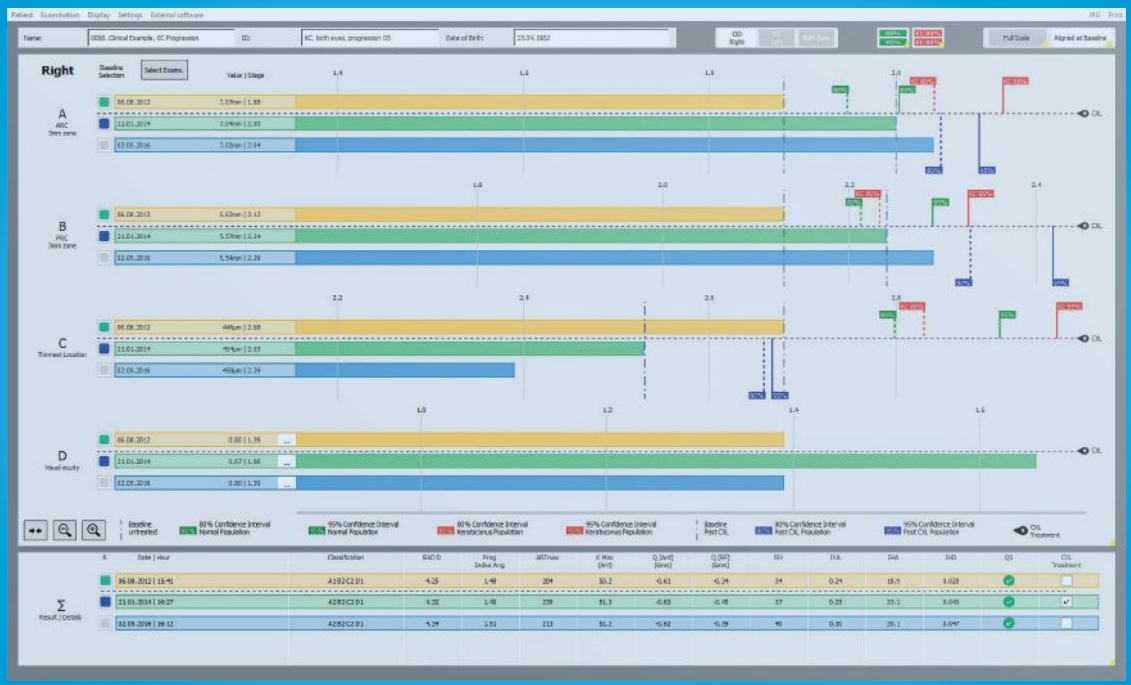
Our patient reported significant improvement in comfort with scleral lens fitting with an extended wear application. He was cautioned that significant mucin would build up under the lens, which would look terrible but was not harmful. The lens was removed in office every several days and cleaned and sterilized. Systemically, he was started on mycophenolate, since the more commonly used methotrexate is contraindicated in someone with liver-concerning diseases, such as hepatitis C. It is our recommendation that 24/7 application of the scleral lens, as well as aggressive oral and systemic therapies and comanagement, should continue until the guttering has filled in and the eyes are no longer at risk for perforation. This is not a fast process and may take months to see improvement. RCCL

1. Singh G, Salvador VB, Bagchi A, Tushabe R, Abrudescu A. Rheumatoid arthritis-associated corneal ulceration with superimposed infection by methicillin-resistant Staphylococcus aureus: a complicated type of corneal melt. Am J Case Rep. 2014 Nov 27;15:523-5.

2. Sule A, Balakrishnan C, Gaitonde S, et al. Rheumatoid corneal melt. Rheumatology, 2002; 41(6): 705-6.

Photo courtesy of Sara Downes, OD

Keratoconus Progression at a Glance!



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