JANUARY/FEBRUARY 2018

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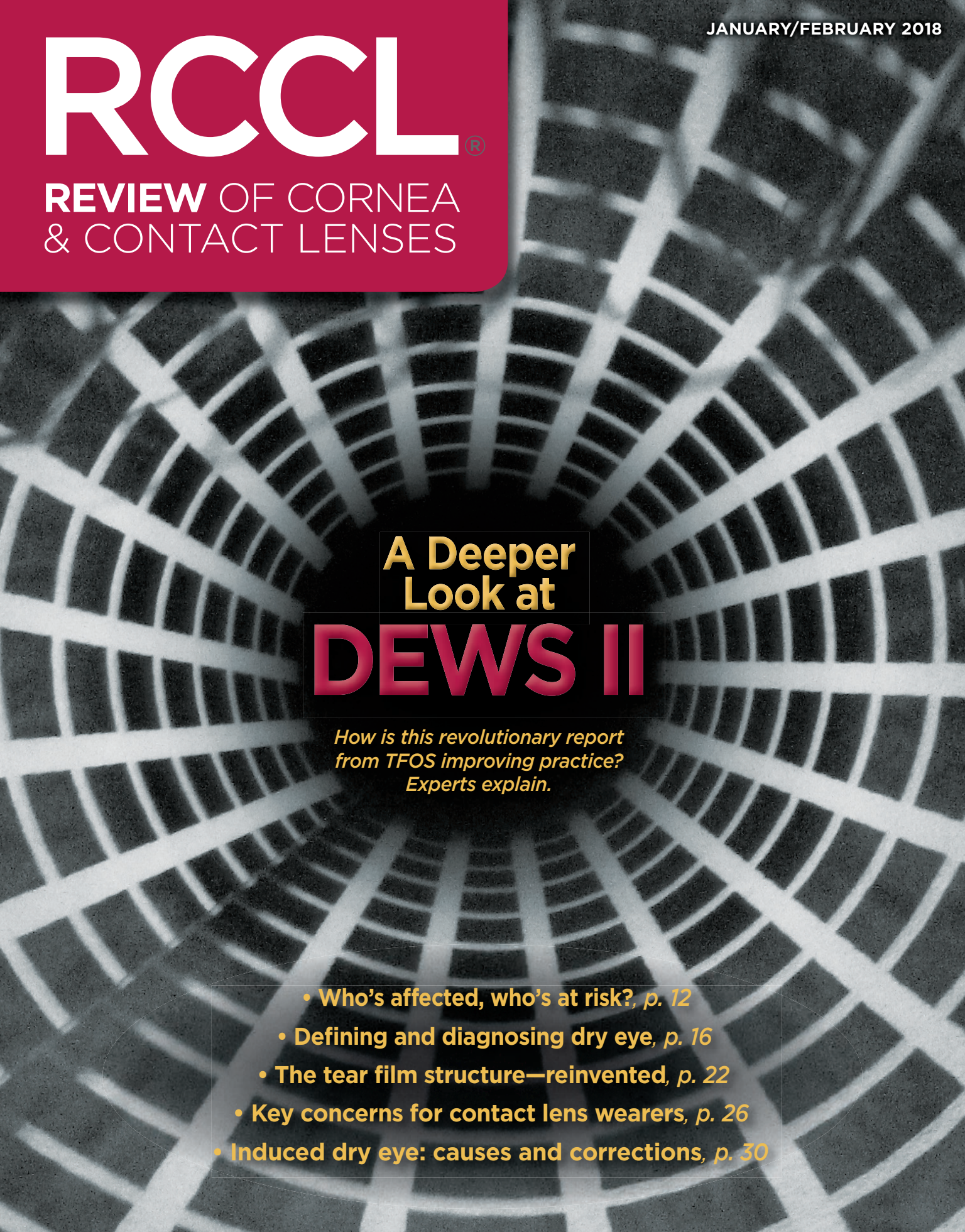
REVIEW OF CORNEA & CONTACT LENSES



A Deeper Look at DEWS II

How is this revolutionary report from TFOS improving practice? Experts explain.

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[2] Compared among CooperVision silicone hydrogel contact lenses. Data on file.

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Review of Cornea & Contact Lenses | January/February 2018

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IN BRIEF

■ Adjunctive **amniotic membrane transplantation** and **intraoperative mitomycin C (MMC) can reduce recurrence after pterygium surgery**. Recurrence can be as high as 88% after simple excision involving an uncovered bare sclera. In comparison, this noncomparative retrospective study showed that of the 556 eyes of 535 patients that had pterygium surgery performed by the same surgeon and used a cryopreserved amniotic membrane and MMC, **only 3.6% had corneal recurrence and 2.2% had conjunctival recurrence**.

Rosen R. Amniotic membrane grafts to reduce pterygium recurrence. Cornea. 2018;37(2):189-93.

■ A new meta-analysis reveals that **standard corneal collagen crosslinking** (epithelium-off CXL) was **more effective in decreasing the maximum keratometry** than transepithelial CXL in patients with keratoconus. The researchers evaluated three studies with a total of 244 eyes—111 in the standard CXL group and 133 in the transepithelial CXL group. They found a **mean keratometry difference of 1.05D** at least 12 months post-procedure, **in favor of standard CXL**. At the same time, transepithelial CXL provided slightly better corrected distance visual acuity. Both had similar safety.

Li W, Wang B. Efficacy and safety of transepithelial corneal collagen crosslinking surgery versus standard corneal collagen crosslinking surgery for keratoconus: a meta-analysis of randomized controlled trials. BMC Ophthalmol. December 28, 2017. [Epub].

■ Italian researchers recently discovered **obstructive sleep apnea (OSA) was 10 to 20 times more prevalent** in study patients with **keratoconus** compared with the rate found within the general population. After studying 50 patients diagnosed with keratoconus using home overnight polysomnography, they found 38% had OSA—a mild form in roughly half of study participants. They did not find any statistically significant differences in corneal parameters or keratoconus severity between patients with and without OSA and patients with different degrees of OSA severity.

Pedrotti E, Demasi CL, Fasolo. Obstructive sleep apnea assessed by overnight polysomnography in patients with keratoconus. Cornea. January 9, 2018. [Epub ahead of print].

ODs Rally for FTC Contact Lens Rule Workshop

More than a year after proposing changes to the Contact Lens Rule, the Federal Trade Commission (FTC) is answering pushback from the American Optometric Association (AOA), lawmakers, practitioners and other advocates with a public Contact Lens Rule Workshop on March 7 in Washington, DC. The gathering, designed to discuss contact lens marketplace competition, consumer access, prescription release and portability, and other contact lens-related subjects, will feature panelists, public comments and feedback.

A persistent advocate for contact lens patient health and safety, the AOA says it will be an active participant in the upcoming workshop.

"During the past year, the AOA and our supporters have underscored that our regulatory agencies should take a closer look at those online contact lens retailers who are breaking the current laws instead of supporting more unnecessary bureaucracy," says Christopher J. Quinn, OD, AOA president. "AOA will carry this message forward and has been working quickly to prepare for this workshop."

Among the proposed changes is a mandate that eye care practitioners maintain a signed agreement of prescription dispensation for contact lens patients for three years.

"I can't help but feel the FTC proposed paperwork mandate is somehow a diversionary tactic supported by companies like 1800-Contacts, designed to keep organized optometry away from working on the real issue of protecting patients from unscrupulous business tactics," says Justin Bazan, OD, of Park Slope Eye. "I understand the FTC is focused on ensuring a competitive marketplace, but it cannot be done without also safeguarding the eyes of our patients."

The change would drive a wedge in the doctor-patient relationship and have a huge impact on the bottom line. The FTC estimates it would cost the industry roughly $10.5 million, while the AOA cites a study that suggests an unacceptable burden for ODs, with potential costs to a one-doctor, one-support staff practice as high as $18,795 in the initial year, if finalized.

To rally the profession, the AOA has issued a call to action to ensure at least one OD from each state attends the meeting to create a united front, according to Dr. Quinn.

"One thing that is critical is that we mobilize to ensure that the optometric profession's full perspective and range of expertise is included in every aspect of the discussion," Dr. Quinn says. "Those who want to undermine optometry and patient care will be there in force, and optometry needs to have a stronger presence."

"There will be strict limits on participation, and not every doctor will gain recognition during the limited times for open discussion," Dr. Quinn adds. "But an engaged, nationally representative group of doctors on hand will deliver a powerful message to the FTC."

"This workshop absolutely requires a strong showing from organized optometry," says Dr. Bazan. "As an optometrist, I feel it's a duty to my profession to, at a minimum, let the FTC know how I feel."

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Depression and Anxiety Show Dry Eye Correlation

A recent study found a correlation between dry eye and non-ocular comorbidities such as anxiety and depression.[1] This suggests that, for some patients, dry eye symptoms may stem from a condition unrelated to ocular surface health. For practitioners, this could explain why some dry eye cases do not respond to topical dry eye treatment.

"It's a great point to note that ocular pain and depression/anxiety are correlated with non-ocular pain," says Bill Potter, OD, chief of Optometry and Contact Lens Services at Millennium Eye Care in West Freehold, NJ. "Perceptions of pain and associated mental health issues vary tremendously by age, culture, sex and more. Some of it is due to induced biochemical changes and some is due to the way that we are hard-wired."

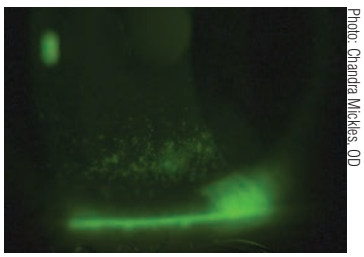

Photo: Chandra Mickles, OD

Depression and anxiety may be associated with dry eye, similar to other systemic conditions like Sjögren's.

Researchers used the Pearson correlation coefficient to evaluate the association of dry eye symptoms and neuropathic-like ocular pain features, chronic pain conditions, depression and anxiety in 233 patients.

Coming into the study, about 40% of patients had mild or greater dry eye symptoms and 12% had severe symptoms per the Dry Eye Questionnaire. The patient population was predominantly female to counterbalance a previous study that looked at a mostly male population. However, results were consistent between both studies, showing notable correlation between dry eye symptoms and neuropathic-like ocular pain (burning and sensitivity to wind, light and temperature), non-ocular pain conditions (arthritic pain, back pain and headaches), depression and anxiety. According to the study, the results indicate "the link between dry eye symptoms and pain elsewhere in the body is robust," and suggest that "optometrists need to redefine dry eye and separate those who have ocular surface dryness from those whose dry eye symptoms are driven by somatosensory dysfunction such as neuropathy."

"Dry eye with systemic comorbidity is a classic example of how we need an integrated approach, mental health and systemic pain control included," says Dr. Potter. "Although there is a trend toward optometrists doing more traditional primary medical care, we can't do it all. Teamwork with other specialists is key."

While dry eye therapies target tear function, inflammation and ocular surface anatomy, patients with both dry eye symptoms and non-ocular pain conditions may benefit more from treatments that focus on reducing the excitability of somatosensory function, the study says.

For future studies, Dr. Potter suggests identifying psychological or systemic pathophysiologic profiles that would indicate patients at greater risk for progression. RCCL

1. Chang VS, Rose TP, Karp CL, et al. Neuropathic-like ocular pain and nonocular comorbidities correlate with dry eye symptoms. Eye & Contact Lens. December 7, 2017. [Epub ahead of print].

By Joseph P. Shovlin, OD

The Clinical Implications of DEWS II

Highlights: a retooled classification system and elevated awareness of neuropathic pain.

The first Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS), published in 2007, brought much-needed attention to the complex disease we call dry eye. The report emphasized the significant morbidity associated with an inflammatory process and recognized the quality of life issues that pose a tremendous burden to most patients with dry eye. As a result, DEWS sparked much interest in the research community and generated additional questions that beg to be answered.

This past July, TFOS released the second DEWS report (DEWS II), which expands on everything learned from the past 10 years of research. The updated definition of dry eye stresses its multifactorial nature as a disease. Also, the loss of homeostasis in the tear film is the central pathophysiological notion that defines dry eye disease (DED).[1] Here are some important aspects of DEWS II and the clinical implications they bring.

THE TOP TWO

I find two aspects of the report most intriguing: the new classification scheme and the exhaustive discussion on the neurosensory component of dry eye and neuropathic pain in general.

One way in which DEWS II expands upon its predecessor is with the introduction of a slightly different classification system that allows us to identify the essential component to effectively treat a patient's condition.[2,3] Rather than taking a shotgun approach to treating DED, clinicians can now directly address an individual's specific problems. This may help explain why traditional treatment strategies have not worked for some patients in the past.

Additionally, DEWS II reflects current research by establishing biomarkers that are critical in DED pathogenesis.[2,4] It retains the two major divisions in DED—evaporative and aqueous deficient—but stresses that both play a role the majority of time, with one likely driving the other.[2] Cosmetics, contact lenses and the use of medications, both topical and oral, remain significant contributors in iatrogenic dry eye.[2]

According to DEWS II, neurosensory abnormalities also play a crucial role in DED, and the discussion includes neuropathic pain.[4] For some patients with significant symptoms but no signs of true DED, pain management would likely be the most appropriate treatment option.

PAIN UNDER THE MICROSCOPE

An increase in ocular surface inflammation and osmolarity results in peripheral nerve damage.[1,4] This propels additional sensitizing of the corneal nerves, causing the neurons to experience a decreased threshold and increased responsiveness to stimulation (i.e., wind or cold).[4] Differentiating nociceptive pain from neuropathic pain in DED is fundamentally essential for successful treatment. A key component of neuropathic pain is the lack of objective signs in patients with severe DED-like symptoms.[2-4] These patients don't respond with appropriate relief when topical anesthetics are applied to the eye. They also often have pain elsewhere in their body.[2,4]

Beyond DEWS II, further research is needed to expose all the components in the development of neurosensory changes seen in dry eye.

Standard treatments for neuropathic pain consist of increased intake of antioxidants and off-label use of anticonvulsants, tricyclic antidepressants, opioids or neuromodulators.[4] In particular, the use of topical lacosamide 1% has received some attention along with the use of scleral lenses for drug retention. However, guidelines on how to best manage neuropathic pain that manifests with dry eye-like symptoms are still sparse.

Kudos to the consensus team for their fabulous work with TFOS DEWS II. We look forward to further research in our quest to better understand the tear film's ecosystem and new strategies to help us manage this complex disease. RCCL

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2. Guttman Krader C. TFOS DEWS II report introduces new patient classification scheme. 2017. ophthalmologytimes.modernmedicine.com/ophthalmologytimes/news/tfos-dews-ii-report-introduces-new-patient-classification-scheme. Accessed December 18, 2017.

3. Andersen HH, Yosipovitch G, Galor A. Neuropathic symptoms of the ocular surface: dryness, pain and itch. Curr Opin Allergy Clin Immunol. 2017;17(5):373-81.

4. Belmonte C, Nichols JJ, Cox SM, et al. TFOS DEWS II pain and sensation report. Ocular Surf. 2017;15(3):407-37.

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By David Kading, OD and Mile Brujic, OD

Sclerals: A Blueprint for Beginners

With simple in-office tools and a few reliable lab partners, you'll be on your way.

Not only have scleral lenses altered the landscape of custom and specialty lenses, they have begun to compete with mainstream contact lens options. Not long ago, we would fit scleral lenses only for the worst of the worst keratoconus or transplant patients. Now, we are reaching for scleral lenses on a daily basis. The benefits and features scleral lenses can bring to both the patient and the practice are phenomenal and well worth exploring.

But like most things, scleral lenses have a range. The basics of scleral lenses can be taught in a few hours and can get a fitter up and running with the lenses on some of their easier patients. The more advanced fitting techniques can be explored in endless detail, and we are always learning new things from the fits and patients we encounter on a daily basis.

This beginner blueprint can help you get started fitting scleral lenses in your practice.

WHAT YOU NEED

The first step in integrating scleral lenses into your practice is gathering the tools of the trade before ordering a fitting set or a lens for a patient. Although every contact lens fitter has their own preferences when it comes to the tools they use, most would agree this basic list includes the essentials:

- Small plunger for removal of lenses.
- Large plunger for insertion of lenses (*Figure 1*).
- Non-preserved saline solution to fill the bowl of the lens for insertion.
- Sodium fluorescein inserted in the bowl of the lens to help visualize fit.
- Slit lamp.
- OCT with anterior segment abilities (optional, but useful).

FITTING SET

Scleral lenses cannot be ordered empirically and must be fit using a diagnostic lens. Because they are fit with vault over the cornea and land on the sclera, we need to see a lens on the eye; our modern measurement capabilities are still too variable to ensure a proper fit with measurements alone. Future technologies may soon address this.

A good place to start is the fitting set provided by your gas permeable laboratory. You can also ask colleagues about the fitting set they use; if you choose to use the same fitting set as a colleague, you will have the same language if you need advice. First-time fitters would do well to choose a fitting set that is simple, has great education in video form, has plenty of support from people who have fit the lens.

Some lens types come with 36 to 50 lenses in their fitting set. Although this may allow you to fit a few more patients than a fitting set with only eight lenses, it may be too daunting at first. We personally use a fitting set that has 12 lenses. For us, a more simplified approach speeds up the fitting process.

Video education is ideal for clinicians looking to learn and enhance their fitting. Pictures rarely provide the perspective that you see with your slit lamp and dynamic movements. Look for guides that include training videos that will help to increase your confidence—you will also want videos that allow you to refer back to them after you have fit the lens a couple of times.

INITIAL HURDLES

Starting to fit scleral lenses can seem intimidating, especially if you have

Fig. 1. A large plunger is a helpful tool to insert scleral lenses.

SUPPORTING ACTOR

A laboratory's job is to make you more successful—they are your partner. If the lab overcomplicates things or does not give you the support you need, it is time to find a new laboratory. Make sure that they support you as you start this new adventure with scleral lenses.

never done it in a workshop setting; however, a plethora of online education can guide you.

Before seeing any patients, you need to practice. You can place lenses on your own eyes and other team members' eyes. Do lens evaluations on them with your slit lamp and role-play the fitting process. Then, remove the lenses. You should have plenty of experience with inserting and removing the lenses before you see your first patient.

FITTING PEARLS

- A scleral lens generally settles onto the eye by about 100µm. That means if you want a lens to be 100µm above the cornea, you will be looking for 200µm of clearance initially.
- A slit lamp allows you to get an estimation of this, and an OCT will likely increase your accuracy substantially.
- We know the limbus is a critical part of the cornea for the creation of stem cells. As such, our approach is to never touch the limbus (*Figure 2*).
- We make sure the periphery of the lens lands on the tissue as much as possible. Sometimes this means modifying the curve so that it doesn't dig into the conjunctiva or lift off, thus placing more pressure. Spreading the pressure across a larger area of the lens evens out the weight of the lens.
- Clinicians new to scleral lenses can access the GP Lens Institute's scleral lens tools and resources, including troubleshooting FAQs, lens fit scales and more by, visiting: www.gpli.info/scleral-lenses.

Your team should train with you in the care and handling of lenses, as well as insertion and removal. While you should do the training on the first two to three patients, you can have a team member join you so they can learn alongside of you.

GETTING THE OFFICE READY FOR SCLERALS

If you are the first in your office to fit scleral lenses, it is important to prepare your team. Everyone needs to know what scleral lenses are, how they work, why they are fit on some patients instead of other lens modalities, why they are so expensive and how to bill for them, to name only a few key educational needs. Team members will also need to be prepared for the added patient education and questions such as what patients can expect from wearing them, initially and long-term, and what the aftercare is going to look like. We suggest creating a how-to manual for your team's reference.

When billing for these specialty lenses, you must call a patient's insurance company ahead of time, or look into whether they have coverage so that you are able to estimate the patient's out-of-pocket costs.

FITTING BASICS

Generally speaking, we feel that the vast majority of scleral lens fittings follow these three principles:

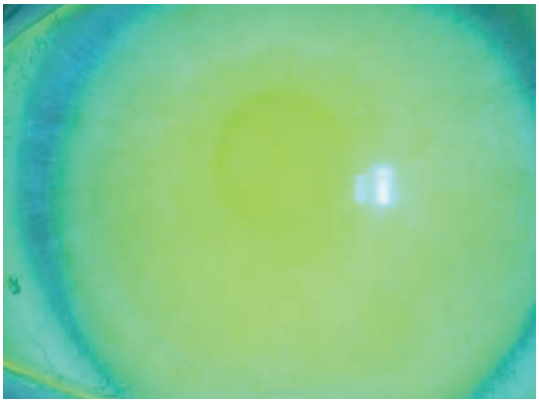


Fig. 2. This scleral lens shows limbal bearing, which should be avoided.

1. Vault over the central cornea (100µm to 300µm).
2. Clear the limbal transition area.
3. Land the lens as tangentially as possible on the conjunctiva/sclera.

Scleral lenses are intended to vault over the central cornea, but not too much and not too little. If there is too much clearance, the cornea may not get the oxygen it needs; if the lens does not have enough vault, it may land directly on the cornea.

Becoming proficient with these three principles takes time. Your laboratory can help you troubleshoot issues that arise during fitting. Take pictures and video whenever you can to show the lab.

Getting into fitting scleral lenses doesn't need to feel like rocket science. Attending conferences and workshops can give you a leg up, as can other online training—and good ol' practice. With a little preparation, you can provide your patients with a wonderful specialty lens fitting experience. RCCL

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

What's New with Uveitis

Statins, dietary supplements and a new way to deliver steroids might become part of your treatment regimen, improving outcomes and reducing risks.

Not much has changed in the management of anterior uveitis over the last several decades. However, researchers have been studying the pathophysiology of the condition to better understand what could alter the disease course. New imaging techniques and drug delivery systems, as well as supplementation and a different class of pharmaceutical, may all one day revolutionize our management strategy for uveitis.

While all of the newer studies have a small sample size, their findings are significant enough to warrant larger studies and further investigation. Here is a look at the latest science enriching our understanding of uveitis.

LEAKY VESSELS

In one study, researchers used ultra-widefield angiography to evaluate 65 eyes in 33 patients diagnosed with anterior uveitis. At the time of angiography, 42% still had active uveitis, while the remaining 58% were classified as inactive and treatment had been discontinued for two weeks to six months (average of 2.4 months). Inactivity was based on no or rare cells in the anterior chamber at the time of imaging.[1]

Ultra-widefield angiography has the capability to image 150° to 200°, allowing for peripheral retinal evaluation. Traditional fluorescein angiography typically images only 30° to 55°. This study found that 42% (27 eyes) had peripheral vessel leakage, including 12 of the eyes that had been classified as inactive.[1,2] These findings altered the management strategy, as those inactive with peripheral leakage were restarted on traditional anterior uveitis treatment.

These findings challenge the classical thinking that the inflammation is limited to the anterior uvea and our ability to determine if it is truly quiescent. The detection of such vascular changes may alter the assessment of disease activity and management decisions.[1]

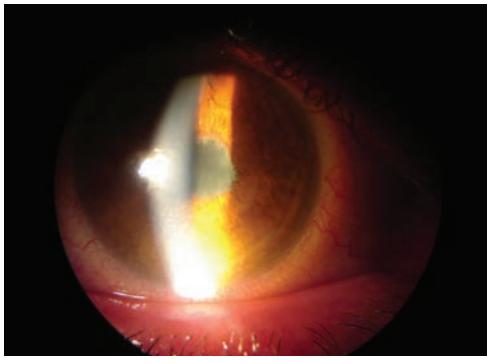


Photo: Paul C. Ajamian, OD

Patients with anterior uveitis are often treated with a potent topical steroid, which can cause an increase in intraocular pressure. New treatments under investigation may avoid this potential adverse effect.

VITAMIN DEFICIENCY

Research demonstrates vitamin D can reverse uveitis in animal models by inhibiting uveal T-lymphocytes, and a small study evaluated serum vitamin D levels in 20 patients with anterior uveitis and 20 controls.[3] Vitamin D helps to regulate the immune system, and a deficiency is linked to cardiovascular disease, cancer, allergies and autoimmune disorders, to name a few.[3,4] In this study, fasting venous blood was collected from 20 patients with active anterior uveitis classified as either idiopathic or HLA-B27 positive. Their vitamin D levels were compared with 20 age-matched controls. The researchers found statistically significant lower levels of vitamin D in the group with acute anterior uveitis compared with the vitamin D levels of controls.

Although not an outcome measure of the study, once vitamin D supplementation was initiated, the patients had no recurrence of uveitis.[3] Further studies are needed, but these findings suggest vitamin D supplementation may play a role in future management of anterior uveitis.

MEDICAL MANAGEMENT

Statins, commonly used in the management of hypercholesterolemia, have been shown in animal models to have anti-inflammatory effects on induced uveoretinitis and rheumatoid arthritis.[5] Additionally, a retrospective study in humans showed a decreased risk of uveitis in patients taking statins.[6] To further explore this possible association, researchers enrolled 50 patients with uveitis in a prospective, open-label, randomized study. Of the 50 patients, 45 (90%) had anterior uveitis. All patients received traditional management consisting of local and, when necessary, systemic steroids prescribed at the provider's discretion. Patients were randomized to receive either a placebo or 40mg/day of simvastatin for eight weeks.[5] The researchers found those receiving simvastatin

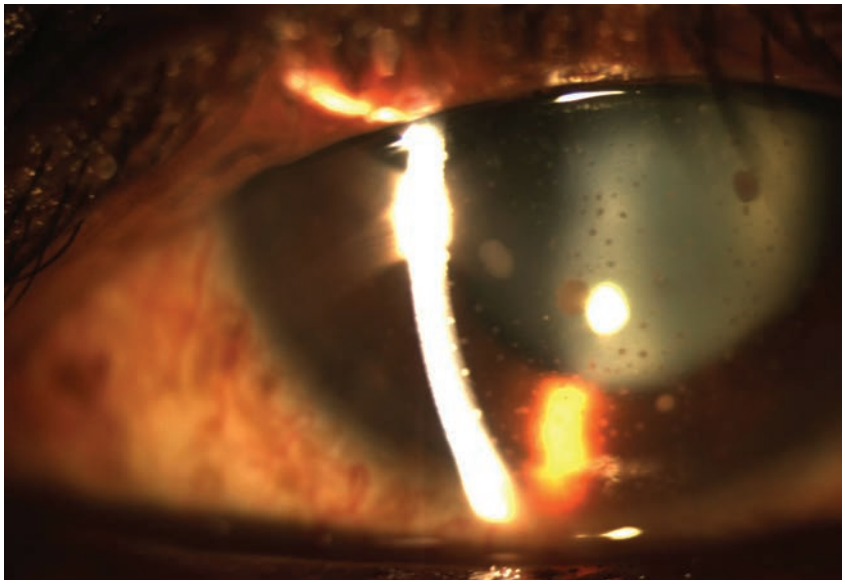

had significantly higher rates of steroid-free inflammation control, greater decrease in anterior chamber inflammation and better visual acuity. The simvastatin was well tolerated and no serious adverse events were reported.[5] Statins exhibit anti-inflammatory properties and modulate the immune system by inhibiting transcription factors and suppressing production of various pro-inflammatory cytokines such as IL-6, IL-8 and TNF-α.[5] Statins are reported to also inhibit leukocyte function antigen-1 from binding, limiting the production of ocular inflammation.[5]

The authors conclude that statins may be beneficial for the management of anterior uveitis.[5] If this does become part of the treatment regimen, eye care providers will need to be reminded of the serious side effects of this class of medications, which includes myopathy, rhabdomyolysis and liver dysfunction.[7]

DRUG DELIVERY

The EyeGate II drug delivery system, which uses transscleral iontophoresis to deliver controlled therapeutic levels of a drug to the targeted ocular tissue, is currently under investigation and is showing promise. This technology was developed at Bascom Palmer Eye Institute and has been used in over 2,000 clinical trials.[8] A low-level electrical current is used to deliver a specific amount of an ionizable drug to the targeted ocular tissue.[8]

One such drug currently under investigation with this delivery system is EGP-437, which administers dexamethasone phosphate 40mg/mL.[8-10] In a Phase III study, patients with anterior uveitis were managed either with traditional therapy or iontophoresis—consisting of two treatments of three minutes/eye. The researchers noted the same rate of response with a total of six minutes of drug delivery vs. traditional drop therapy. This method avoids the shortcomings of traditional eye drop therapy such as poor bioavailability, rapid clearance and poor patient compliance.[8] The researchers did notice the incidence of elevated intraocular pressure was less with the iontophoresis group.[8]



Electronic stimulation of ocular tissues to improve drug penetration—called iontophoresis—may soon be available for anterior uveitis.

While larger clinical trials are needed, the future for novel yet simplified treatments for anterior uveitis looks bright. These studies may one day lead to actionable management strategies to improve uveitis care. RCCL

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The Global Burden of Dry Eye

This pervasive disease flourishes in the presence of MGD, especially in those made susceptible by age, sex, ethnicity and environment. Knowing these risk factors allows earlier intervention.

By Fiona Stapleton, PhD, MCOptom

The Tear Film and Ocular Surface Society's second Dry Eye Workshop (DEWS II) report has redefined how we think about dry eye disease (DED) from diagnostic, pathophysiological and management perspectives. This article explores the clinical implications of new findings on the epidemiology of the disease and how they might help us diagnose and manage DED in new or previously diagnosed DED patients.[1] Additionally, it will cover how these new findings further expose the impact of the disease from individual and societal perspectives.

INTERNATIONAL IMPACT

DED affects tens of millions of individuals around the world, and both its frequency and impact increase with age. Consequently, it is considered a major international health concern. Dry eye is the most commonly reported reason for seeking medical eye care, and up to one in five patients presenting to hospital outpatient clinics or optometry practices experience dry eye.[2-5]

Dry eye has significant socioeconomic implications. In the United States, the average cost of dry eye management is $11,302 per patient and $55 billion overall.[6] While absolute costs vary depending on health care systems and insurance plans, it is clear that DED results in increased healthcare usage and cost. With increased life expectancy and an aging population, the economic and social impacts of this condition are expected to grow substantially.

The most significant societal impact occurs through reduced productivity at work, as well as reduced vision and quality of life for affected individuals.[7,8] Those with dry eye are two to three times more likely to report problems with everyday activities such as reading, performing professional work tasks, computer use, watching television and daytime or nighttime driving.[9-11]

As practitioners, we generally look to optimize static visual acuity, but for our dry eye patients, quality of dynamic vision is compromised. As such, we need to tailor our questioning to focus on the specifics of the visual issue, its impact and its changes with treatment. New technologies such as real-time, smartphone-based data capture capabilities may help in our understanding of the impact of dry eye on quality of life.

EVAPORATIVE IS IMPORTANT

Recent clinical and epidemiological studies have confirmed that most dry eye patients show signs of mixed evaporative and aqueous deficient dry eye, with evaporative dry eye being the most common manifestation.[12-15] Evaporative dry eye is most often associated with meibomian gland dysfunction (MGD). For clinicians, this means taking greater care when examining the eyelids and looking for a short tear break-up time (TBUT), even when the tear volume is normal and no dry eye symptoms exist. One recent study showed that asymptomatic MGD is twice as common as symptomatic MGD, while symptomatic MGD is equally as common in men and women in a Caucasian population.[16]

Another study, based on claims data in the United States, suggests that one of the main risk factors in the development of more severe disease over time is the presence of MGD signs.[17] While still an unproven hypothesis, recognizing signs of MGD early and intervening may limit progression to more severe and symptomatic disease.

PREVALENCE

Determining how common dry eye is depends on how the disease is defined. However, we can make

ABOUT THE AUTHOR

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some broad conclusions based on DEWS II:[1]

• Signs of dry eye, including short TBUT, reduced tear volume, ocular surface staining or lid signs, occur in up to 75% of some populations and are more variable than disease prevalence based on reporting of symptoms.[18] Some signs (e.g., corneal staining) are non-specific and may reflect secondary outcomes of disease or be a consequence of normal aging. The DEWS II diagnostic methodology report describes a pathological cut-off as ±2 standard deviations from the mean in a normal age-matched population, which may help us interpret these findings and apply them in our practice settings.[18]

• The prevalence of DED increases with age, ranging from a 2% increase in prevalence per decade for practitioner-diagnosed dry eye to 10% per decade for disease based on low tear volume. Intriguingly, studies in school children and young adults show unexpectedly high rates of dry eye, perhaps raising the importance of exploring potential risk factors such as digital device use in these populations.

• Women generally have a higher rate of disease than men, although differences between the sexes in prevalence rate become significant with age. There are limited MGD studies stratified by sex and age, and so far the findings for sex are equivocal.

• For disease definitions similar to dry eye, Asian populations have a higher rate than those in Caucasian populations. The reasons for this are unclear, but they may include genetic or environmental determinants.

Techniques such as spatial epidemiology and geographic mapping may help us to understand the impact of broad environmental differences such as climate, altitude, air quality, population density and other human development indices.

• Severe dry eye with major impact on quality of life can affect up to 10% of the population over 50.

WHO AND WHY?

In DEWS II, risk factors are based on how robust the association with dry eye is (consistent, probable or inconclusive) and whether the risk factor is modifiable or non-modifiable. Risk factors are important in patient education, framing triaging questions and directing management strategies such as environmental modification, dietary changes or management of MGD.

Non-modifiable risk factors include age, sex, MGD, Sjögren's syndrome and connective tissue diseases.

Consistent modifiable factors, meanwhile, include androgen deficiency, computer use, certain environmental conditions, contact lens wear, hormone replacement therapy and common medications such as beta-blockers, anxiolytics, antidepressants, cholinergic agonists, isotretinoin and diuretics.

Probable factors are diabetes, thyroid disease, viral infections, allergic conjunctivitis (*Figure 1*), low fatty acid intake and refractive surgery.

A limited number of high-quality studies have looked at factors that predispose patients to more severe disease. One study looked at characteristics associated with worsening dryness symptoms, and the researchers found that more money spent on treatment, a history of severe symptoms and use of systemic beta-blockers were predictors.[17] The study also concluded that worsening vision symptoms were associated with a history of ocular surgery, depression and MGD or blepharitis (*Figure 2*).[17]

A greater emphasis on understanding the natural history of both treated and untreated disease could help us better identify patients likely to progress to more severe disease and learn what benefits early intervention might provide.

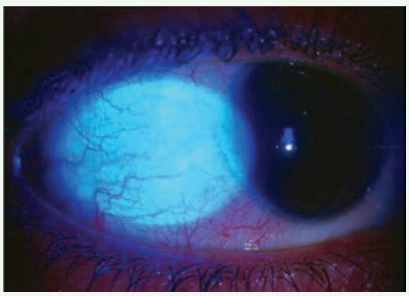

Photo: Greg Black, OD, and Julie Tyler, OD

Fig. 1. Allergic conjunctivitis, shown here, is a probable risk factor for DED.

THE ROLE OF GENES

Genetic susceptibility is believed to be important in the development of DED, but because of its complexity and heterogeneity, little research has been done in this area. Heritability in disorders or traits is often measured in studies of monozygotic and dizygotic twins, which allows us to separate genetic effects, shared environmental effects (events that happen to both twins) and unique environmental effects (events or situations experienced by one twin but not the other). Heritability is measured on a zero to one scale and tells us what proportion of variation in a condition or trait is attributed to genetic factors.

Dry eye signs and symptoms showed moderate heritability (0.3) in a twin study from the United Kingdom (*Table 1*).[19] Interestingly, blepharitis (anterior and posterior) had a strong heritability (0.78), whereas TBUT was entirely attributed to environmental effects and showed no evidence of a genetic contribution. By way of comparison, other studies have shown higher levels of heritability for other ocular conditions such age-related macular degeneration

or increased intraocular pressure.[20] A better understanding these contributions would likely help us to appropriately educate patients and their family members.

Genome-wide studies, in which DNA is collected and analyzed, identify relevant genetic variants in in single nucleotide polymorphism. While conditions such as myopia or glaucoma have been reasonably well characterized in these studies, a broader spectrum of dry eye has yet to be addressed and should be a focus for future studies.

WHAT'S NEXT?

Since the publication of the original TFOS DEWS report, there has been considerable focus on the epidemiology of DED. Despite this, we have seen limited data from regions south of the equator, so large regions of the world are not represented in our current understanding of dry eye prevalence and risk factors. It has been well established that dry eye is common, has a significant impact on patients and has a considerable (and growing) societal cost due to reduced quality of life and reduced work productivity.

Our current understanding of DED risk factors helps us triage our patients and suggest possible management strategies. To better serve our patients, however, we need a more comprehensive understanding of how common the varying severities of dry eye are and the impact of current technologies, such as mobile devices, on the disease. Some evidence from studies in Asia suggests that youth is not protective for dry eye to the extent we would anticipate, but few studies have looked at populations younger than 40. This is clearly an area in need of further study.

Other risk factors such as the impact of climate, environmental and socioeconomic factors also deserve further study. Lastly, and probably most important for ODs, we need to determine whether our management strategies work so that we can modulate signs and symptoms in a predictable way with intervention. Through a better understanding of the natural history of treated and untreated disease, we can predict and better manage patients who will progress to more severe disease. Let's hope we don't have to wait another 20 years for DEWS III to provide the answers. RCCL

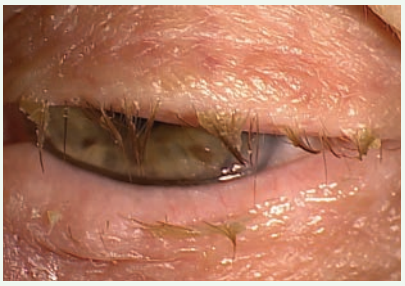

Photo: Paul Karpecki, OD

Fig. 2. A history of blepharitis has been associated with dry eye's worsening visual symptoms.

Table 1. Genetic and Environmental Contributions to Different DED Outcome Variables[19]

0–1 scale, 95% confidence intervals

	Genetic Effects	Shared Environmental Effects	Unique Environmental Effects
Dry eye symptoms within the last three months	0.29 (0.18-0.40)		0.71 (0.60-0.82)
Dry eye diagnosis and current use of artificial tears	0.41 (0.26-0.56)		0.59 (0.58-0.93)
Interblink interval (seconds)	0.25 (0.07-0.42)		0.75 (0.58-0.93)
Tear osmolarity (mOsmol/L)	0.40 (0.25-0.53)		0.60 (0.47-0.75)
Schirmer 1 (mm/5 minutes)	0.58 (0.43-0.70)		0.42 (0.30-0.57)
Fluorescein tear break-up time (seconds)	—	0.30 (0.18-0.40)	0.71 (0.60-0.82)
Signs of anterior or posterior blepharitis	0.78 (0.59-0.90)		0.22 (0.10-0.41)

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Making the Diagnosis with the TFOS DEWS II

Here's how the report's definition, classification system and diagnostic algorithm for dry eye can be used in your practice.

By Jennifer P. Craig, PhD, James S. Wolffsohn, PhD, and Michael T.M. Wang

In 2007, the Tear Film and Ocular Surface Society's Dry Eye Workshop (TFOS DEWS) triggered widespread recognition of dry eye disease (DED), as well as appreciation for its debilitating impact on quality of life and growing prevalence worldwide.[1] In addition to providing the first international consensus summary of the existing literature at the time, the report provided recommendations for future trials and studies. In the 10 years following that initial report, the total number of publications relating to DED almost doubled.[2] The newfound enthusiasm and interest has now spread beyond academia to clinical and industrial sectors, providing aid to the millions with dry eye across the globe.

This past July, the second DEWS report (DEWS II was published.[2] This international collaborative initiative reviewed the thousands of scientific articles published in the field since the original workshop and involved over 150 clinical and basic research experts from 23 countries. The workshop was divided into 12 subcommittees in an effort to generate a consensus understanding of the major aspects of DED. The resulting reports have redefined and reclassified DED, exploring everything from its diagnosis and treatment to recommendations for future clinical trials.[3-12] Here, we provide an overview of the DEWS II Definition and Classification and Diagnostic Methodology reports, and describe how each can be used to help patients in clinical practice.[3,9]

DEFINITION AND CLASSIFICATION

The TFOS DEWS II Definition and Classification subcommittee redefines dry eye as "a multifactorial disease of the ocular surface characterised by the loss of homeostasis, and accompanied by ocular symptoms, in which tear film instability, hyperosmolarity, inflammation, and ocular surface damage, and neurosensory abnormalities, play etiological roles."[3]

Consistent with the original DEWS definition, the multifactorial nature of dry eye is acknowledged in the DEWS II definition.[1] Furthermore, its status as a disease is recognized in order to reflect its significant impact on ocular surface tissues and patient quality of life. New components of the definition include acknowledgement of DED's association with a "loss of homeostasis." This encompasses the diverse range of signs that are possible with ocular surface and tear film imbalance. Also, the phrase "accompanied by ocular symptoms" has been broadened to include symptoms that extend beyond those of ophthalmic discomfort, dryness and visual disturbance. Hence, DED diagnosis requires the presence of both clinical signs and symptoms. Finally, to allow for differentiation of DED from other forms of ocular surface disease (OSD), the key etiological drivers that predispose patients to the self-perpetuating vicious circle of DED have also been included in the definition.[4]

The classification of DED is particularly important in clinical practice, allowing eye care providers to understand where a patient fits within the context of OSD, and thereby tailor dry eye management and treatment

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Dr. Wolffsohn is an associate pro-vice chancellor and professor of optometry at Aston University. He was a chair of the the TFOS DEWS II Diagnostic Methodology subcommittee

Mr. Wang is a doctoral student in ophthalmology at the University of Auckland and a foundation year house officer at Auckland Hospital.

strategies accordingly (*Figure 1*).[3,11] While DEWS II has brought about a patient-centered approach to facilitate the diagnosis of DED patients who exhibit both clinically detectable signs and symptoms, it also acknowledges patients who present with either signs but not symptoms or symptoms but not signs. Without this distinction, the previous DEWS report risked the potential for inadequate management strategies and unrealistic expectations. In studies and clinical trials, inappropriate inclusion of patients without observable dry eye signs or symptoms could also subject new therapies and drugs to unachievable efficacy thresholds during the regulatory approval process, given the difficulty in detecting improvements in clinical signs and symptoms should one or the other fail to exist at the outset.

One example of a case with objective signs, but no subjective symptoms, would be a patient with clinical features of OSD detected incidentally during routine ophthalmic examination, such as before a contact lens fitting or before an operation (*Figure 2*). Another instance would be a patient with reduced corneal sensation, which may arise from neurotrophic conditions. While the treatment for these patients will involve dry eye therapies, differentiating these individuals from those exhibiting both clinical signs and symptoms helps facilitate the development of management plans and targets that acknowledge these differences in baseline status.

The classification system also accounts for patients with symptoms that appear to be incongruent with the signs identified from objective ophthalmic examination. These cases could indicate an early pre-clinical stage, which may require careful monitoring for progression into DED in combination with patient education. However, they may also potentially reflect an element of neuropathic pain, which can be a result of peripheral or central nervous system sensitization.[6] When the ocular surface is not driving the pain reported by

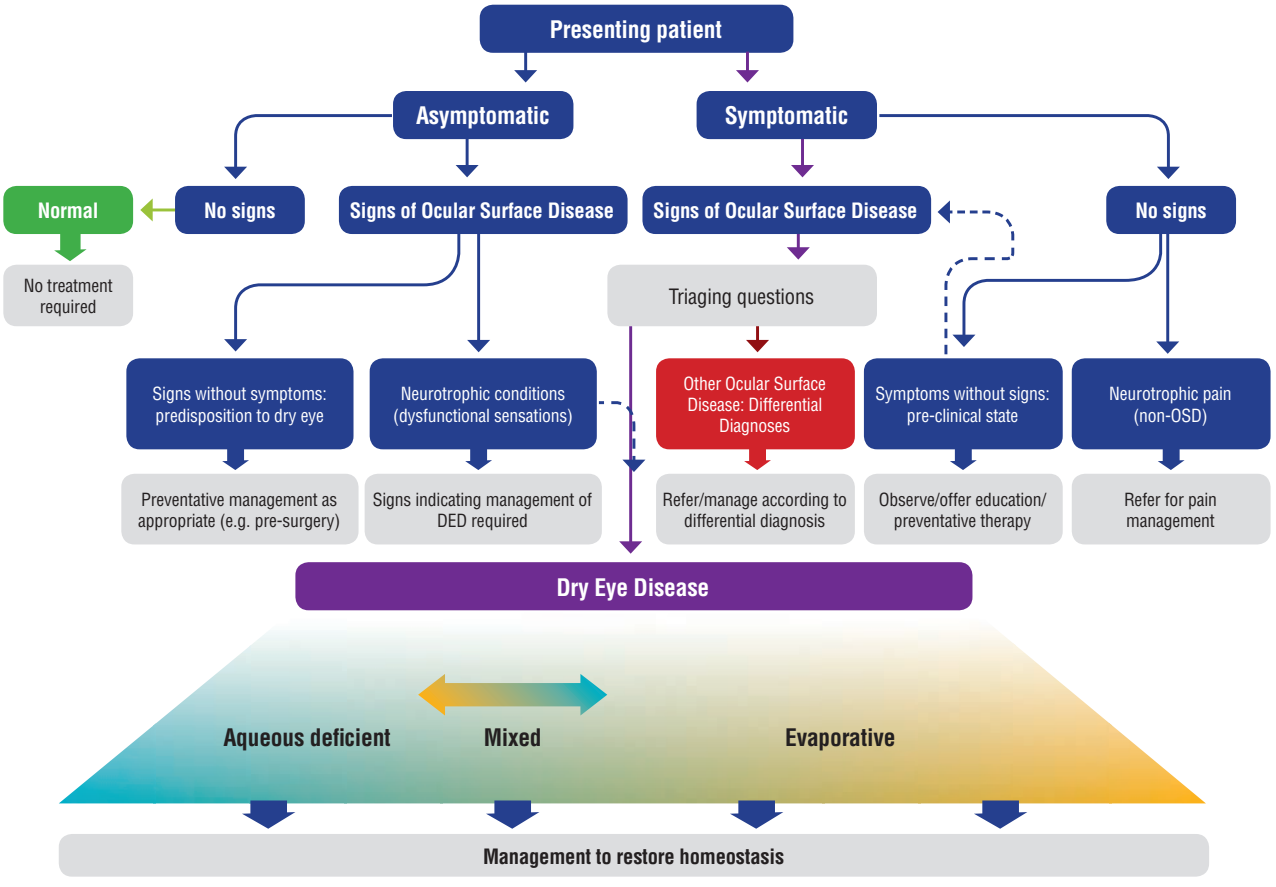

Fig. 1. One important takeaway from the new classification system is its emphasis on mixed forms of dry eye, which is more prevalent than was previously known, according to TFOS DEWS II.

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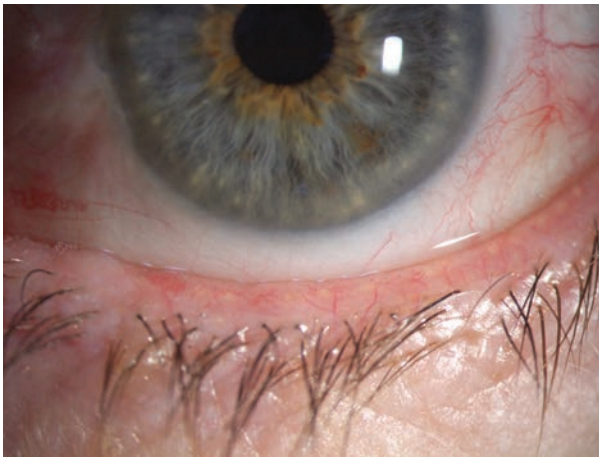

Fig. 2. Signs of blepharitis and low lacrimal lake noted prior to cataract surgery.

the patient, topical treatments are unlikely to provide relief. If this is the case, a referral to a chronic pain clinic may be warranted, as neurosensory abnormalities typically fall outside the scope of conventional therapeutic strategies for DED.

As in prior classification systems, aqueous deficient dry eye and evaporative dry eye are the major subtypes of DED in DEWS II. However, greater emphasis has been placed on the overlap between the two subtypes, given their complex inter-relationship in the vicious circle perpetuating DED. Regardless of etiology, the central mechanism of DED involves hyper-evaporation of the tear film, which results in hyperosmolarity.[4]

In evaporative dry eye (most commonly the result of meibomian gland dysfunction [MGD]), deficiency in the tear film lipid layer compromises its ability to inhibit tear evaporation, thereby causing hyperosmolarity. It is also thought that other factors, such as incomplete blinking, may have an additive effect on evaporative losses from the tear film. In aqueous deficient dry eye, rapid breakup and associated instability of the tear film may exacerbate its evaporative mechanisms.

Aqueous deficient dry eye has multiple causes, including inflammatory infiltration of the lacrimal gland, acinar and ductal epithelial dysfunction. However, blockage of the lacrimal gland's sensory drive and use of systemic drugs including anti-histamines, beta-blockers and diuretics are also recognized causes.[4]

The tear film hyperosmolarity that occurs in both dry eye subtypes can trigger multiple ocular surface inflammation cascades and pathways. The release of inflammatory mediators and proteases can lead to the loss of epithelial and goblet cells, as well as damage to the epithelial glycocalyx. The resulting tear film instability further exacerbates the pre-existing hyperosmolarity, ultimately leading the vicious circle of DED to damage all components of the ocular surface and tear film.[4]

DIAGNOSTIC METHODOLOGY

In the past, reported DED prevalence rates have varied considerably, partly reflecting the heterogeneity in diagnostic criteria applied in the different studies conducted around the world.[7] Consequently, the DEWS II Diagnostic Methodology subcommittee sought to develop a consistent set of diagnostic criteria for DED to be used in future studies.[9] Their report involved a thorough review of the diagnostic accuracy data of validated symptomology questionnaires, as well as ocular surface and tear film measurements from the published literature. This led to a consensus diagnostic battery of tests for DED (*Figure 3*).

In their consensus report, the subcommittee acknowledged the need for clinicians and researchers to differentiate DED from other ocular surface conditions that may confound the diagnosis of DED.

To address this, they developed a series of triaging questions to facilitate the identification of differential diagnoses and comorbidities that may require treatment prior to the management of any residual DED. The triaging questions, listed in *Figure 3*, are designed to be used before the diagnostic battery of tests to encourage differentiation of conditions such as ocular infection and allergy from DED. Any positive responses to the questions should be explored in depth and supplemented with evaluation of relevant clinical signs.

In accordance with the revised DED definition, symptoms and at least one sign of disrupted tear film homoeostasis must be present to reach a dry eye diagnosis.[3] To aid in this process, the subcommittee selected the five-item Dry Eye Questionnaire (DEQ-5) and the Ocular Surface Disease Index (OSDI) as the validated questionnaires of choice in assessing the existence of dry eye symptomology.[9] A positive symptom score requires a diagnostic cut-off score of either ≥6 on the DEQ-5 or ≥13 on the OSDI.

If the patient meets the positive requirement for dry eye symptoms, evaluation should be conducted to confirm whether there are signs of disruption to the tear film or ocular surface homeostasis. This can be confirmed by positive scores in any one of the following three measurements: tear film stability,

tear osmolarity or ocular surface staining.

Whenever possible, tear film stability should be measured using noninvasive methods that reflect mires from the surface of the tear film (*Figure 4*). A diagnostic cut-off break-up time of <10s measured by subjective observation is indicative of tear film instability.

Aqueous sodium fluorescein instillation is no longer recommended for assessing tear film stability because it is associated with tear film destabilization, which artificially decreases breakup time measurements. A minimal amount of fluorescein can be applied via a wetted strip, but only if a noninvasive method is unavailable. In these cases, excess fluid must be shaken off the strip before applying it to the temporal canthal region, and the fluorescein break-up time measurement should be recorded with the aid of a yellow barrier filter to optimize visualization.

In clinical settings, tear osmolarity is commonly measured with the TearLab osmolarity test. With this instrument, a diagnostic cut-off value of ≥308mOsmol/L in the eye with the higher osmolarity, or an interocular difference in osmolarity of >8mOsmol/L constitutes an ocular surface homeostasis disruption.

Ocular surface staining with both sodium fluorescein and lissamine green dyes is assessed under slit lamp biomicroscopy, again with a yellow filter, to optimize visualization of fluorescein. Positive staining is indicated by any one of the following: >5 spots within the cornea, >9 spots in the conjunctiva or lid wiper epitheliopathy that extends at least 2mm along the length of the lid margin and at least 25% of the width (*Figure 5*).

Should DED be confirmed, it is important to determine the relative contribution of aqueous deficiency and hyper-evaporative mechanisms to appropriately tailor therapeutic choices the needs of the individual

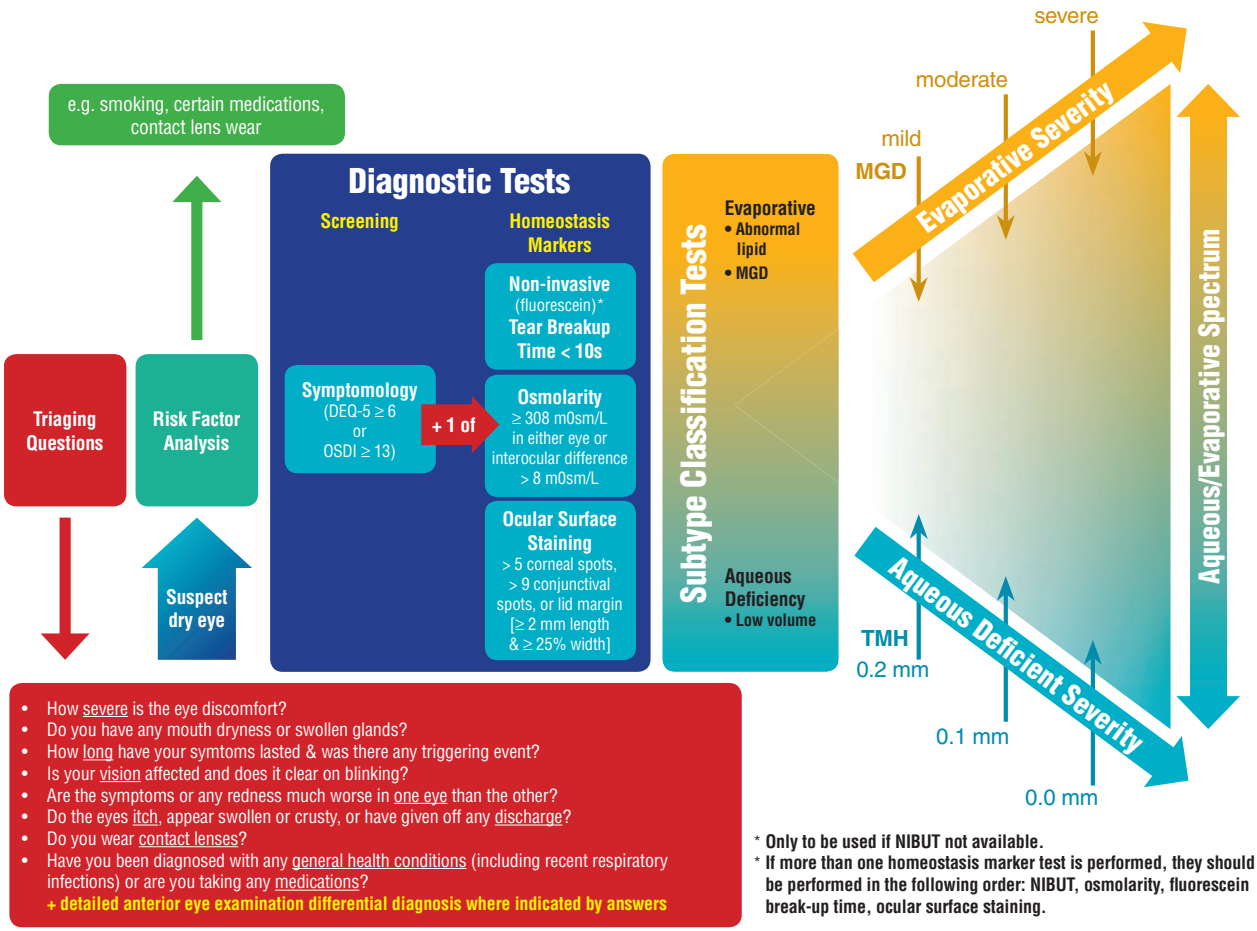

Fig. 3. The TFOS DEWS II diagnostic algorithm prioritizes the role of triaging questions in a dry eye work-up.

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Fig. 4. Mires reflected from the tear film surface allow measurement of tear stability noninvasively.

patient. Tear meniscus height measurement is the preferred noninvasive diagnostic test for aqueous deficiency, with a value of <0.2mm suggesting a tear-deficient state. While other tests such as the phenol red thread test and the Schirmer's test also offer an indirect measure of tear volume, they are not recommended because of their invasive nature. Measurements recorded under topical anesthesia are not suitable replacements, as they are neither reliable nor repeatable.[9]

MGD is considered the leading cause of evaporative dry eye, and therefore gland morphology and function warrants careful evaluation.[14-17] Infrared meibography can be used to assess morphology, and gland function can be directly assessed with the Meibomian Gland Evaluator (TearScience) diagnostic expression or by applying gentle digital pressure. Meibomian gland function can also be indirectly assessed by looking at the quality of lipid layer patterns interferometrically, either with qualitative instruments or with quantitative instruments.

With the revised dry eye definition and classification scheme, as well as the newly developed diagnostic criteria, the hope is that clinicians will be able to better tailor management plans towards the unique needs of their patients and set realistic treatment expectations. Additionally, these guidelines may assist researchers in defining enrollment criteria for participant recruitment in clinical studies and serve as a useful reference for regulators involved in the approval of novel dry eye therapies. RCCL

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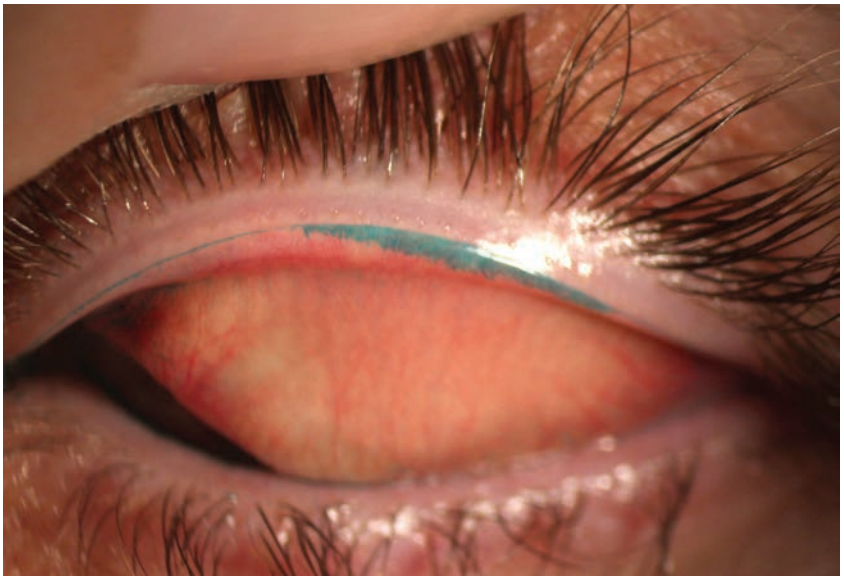

Fig. 5. Lid wiper staining with lissamine green indicates ocular surface damage.

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The TEAR FILM: More Complex Than You May Realize

What we once considered a three-part structure really has two highly interdependent layers in tenous balance, vulnerable to osmolarity and inflammatory changes.

By Lakshman Subbaraman, PhD, BSOptom, MSc

Dry eye disease (DED) affects millions of people and is one of the most frequent causes of patient visits to eye care practitioners.[1] Furthermore, moderate to severe forms of DED are associated with a significant amount of pain, which limits the performance of day-to-day activities, leading to poor general health and, often, depression.

To increase our understanding of DED and better serve these patients, the Tear Film & Ocular Surface Society (TFOS) conducted the TFOS Dry Eye Workshop II (TFOS DEWS II). The Workshop, comprised of 150 clinical and basic science research experts from around the world, addressed various aspects of DED, including a significant reassessment of the tear film.[2]

A stable tear film is an indicator of a healthy ocular surface, primarily because it provides a refracting surface for light entering the eye and creates a safe and lubricious environment for the ocular surface tissues. Because DED is characterized by significant changes to the structure and function of the tear film, clinicians must be aware of these changes and be prepared to diagnose DED in patients who present with tear film concerns.

The TFOS DEWS II tear film report provided a detailed review of the biophysical and biochemical properties of the tears, translational dry eye tear film animal models and non-pathological factors that can impact the tear film. One of the most poignant findings of the report is the loss of tear film homeostasis as a unique characteristic of DED. Specifically, the mechanism of DED is believed to be due to evaporation-induced tear film hyperosmolarity, which damages the ocular surface by inflammation, leading to the disease. Not surprisingly, the major cause of evaporative dry eye is meibomian gland dysfunction.

This summary of the TFOS DEWS II tear film subcommittee report can help you better understand the structure and functions of the tear film, the biophysical and biochemical properties of the tear film in DED—and what it all means in your clinic.

TYPES AND STRUCTURE

Based on the stimulus for tear production, research has broadly classified tears into four types: basal, reflex, emotional and closed-eye.[3] Basal tears typically coat the eye and, in DED, are deficient. Reflex tears are produced upon stimulation of the ocular surface (e.g., vapors produced when peeling an onion) or when the reflex arc is stimulated (e.g., by nasal stimulation of the sneeze reflex). Emotional tears are also produced upon stimulation, but the stimulus here is emotions such as sadness or happiness. Closed-eye tears are those that can be collected from the ocular surface immediately after a period of sleep. Basal, reflex and emotional tears are produced mainly from the lacrimal glands via the neural arc, but differ in their protein concentration.[3] The composition of closed-eye tears differs from other types as they contain an increased amount of serum-derived proteins that leak from the conjunctival blood vessels.

Historically, the tear film has been viewed as a tri-layered structure comprised of the outermost lipid, middle aqueous and an inner mucin layer. However, enough evidence has been generated over the past few years to suggest that the tear film is a bi-phasic structure composed of an outer lipid layer overlying a mucoaqueous phase.[2,4]

BIOCHEMICAL MEASUREMENTS IN DED

The tear film lipid layer is derived from meibum secreted from the lid margins and is spread onto the

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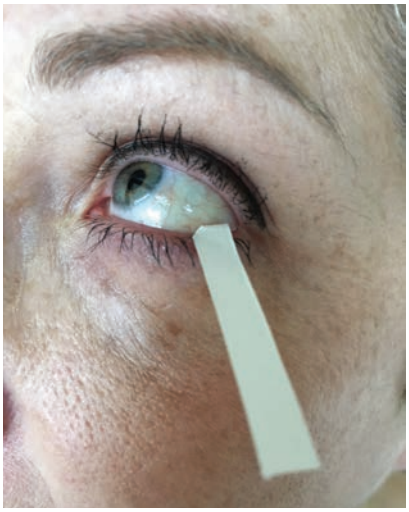

Fig. 1. A Schirmer strip is placed in the lateral one-third of lower eyelid to collect a tear sample.

tear film with each blink, driven by surface tension forces. The lipid layer is crucial for stabilizing the tear film and is thought to play a key role in preventing tear film evaporation. Studies show that the presence of only some lipids will retard tear film evaporation; thus, it may be that the lipid layer, in combination with other components of the tear film, helps to prevent water evaporation.[2,5-7]

The lipid layer is composed of several non-polar and amphiphilic (polar) lipids. The polar lipid family (O-acyl)-hydroxy fatty acids appear to be important in the spreading of the whole lipid layer over the muco-aqueous layer.[2] However, the role of other polar lipids, such as phospholipids, is less clear. Furthermore, the TFOS DEWS II report showed that tear lipid profiles are highly variable between studies and that further investigation is warranted to understand the reason behind this variability.[2]

The mucoaqueous phase of the tear film is composed of at least four major mucins and more than 1,500 different proteins and peptides. Mucins are highly glycosylated proteins that help to hydrate the tears. Decreased MUC5AC expression in DED has been a consistent finding, and research suggests the deregulation of mucin synthesis can be an important factor in ocular surface disease.[8-11] Several of the proteins and peptides found in the muco-aqueous phase have been shown to change with DED. Despite the fact that the protein concentration changes significantly in dry eye conditions (for more than 75 extracellular proteins and 15 intracellular proteins), no definitive set of proteins or changes in protein levels have been validated to help in diagnosis.[2] Commercially available kits to detect tear film biomarkers include Inflammadry (Quidel) to test matrix metalloproteinase-9 and TearScan Lactoferrin Diagnostic Test Kit (Advanced Tear Diagnostics).

While it is widely accepted that the various components of the tear film—including lipids, proteins, mucins and salts—play a critical role in preventing tear film evaporation and collapse, the report suggested that further studies are warranted to confirm or deny this concept.

BIOPHYSICAL MEASUREMENTS IN DED

Tear production, turnover and volume can be determined using several methods; however, the correlation between these tests is limited.[12] Thus, clinicians should perform a combination of tests to ensure a reliable DED diagnosis.[13] The phenol red thread test is a measurement of tear volume or change in tear volume with time, wherein the clinician observes the amount of wetting of a phenol red dye-impregnated cotton thread placed over the inferior eyelid.[14] A more commonly used diagnostic tool, the Schirmer test is a measure of tear production using the wetting of a standardized paper strip (*Figure 1*).[15] Traditionally, clinicians perform the Schirmer I test without anesthesia to measure reflex tearing.

A variation of the Schirmer I test involves the use of a topical anesthetic and measures the tear basal secretion; still, a contribution from reflex tearing cannot be entirely disregarded when employing this testing variation.[16] Tear clearance rate is the rate at which the tear film or an instilled marker of tears is removed from the tear film by dilution or drainage from the tear volume.[17] Tear film dynamics can be assessed by dividing the Schirmer test value with anesthesia by the tear clearance rate (seldom performed in a clinical practice), which provides the tear function index.[18] Research shows this value has a greater sensitivity for detecting DED than either one of these tests conducted alone.[18]

Tear volume, when measured using fluorophotometric methods, demonstrates a normal human tear volume of approximately 8µl ± 3µl.[19] Studies show the tear meniscus height is linearly proportional to the lacrimal secretory rate, and the differences in tear meniscus height and curvature radius can be helpful in the diagnosis of DED

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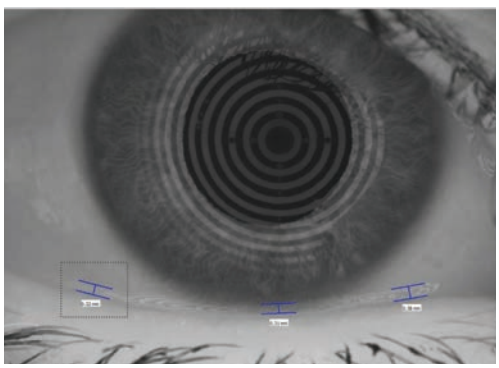

Fig. 2. In this lower tear meniscus image, taken with a Keratograph 5M (Oculus), the nasal, central and temporal tear meniscus heights are indicated by the blue bars.

(*Figure 2*).[19-22] The tear film thickness, now easily measured using optical coherence tomography (OCT), ranges from 2µm to 5.5µm depending on the technique, while the lipid layer thickness ranges between 15nm and 157nm, with a mean of 42nm.[23-25]

Studies show that thinning and tear film break up occur mainly due to tear film evaporation rather than the flow of fluid across the ocular surface.[26,27] Some suggest the entire healthy preocular tear film resists evaporation from the ocular surface, thereby preventing tear thinning. Tear film break-up time (TBUT) measurement may provide insights into the ability of the preocular tear film to prevent evaporative losses. Clinically, although it is relatively easy to determine TBUT, interpreting the result is complicated due to its inherent variability.[28,29]

Several approaches exist to improve the repeatability of TBUT measurements, including taking multiple readings and averaging or selecting a subset of values or by reducing the quantity of fluorescein instilled.[30-33] Whenever possible, clinicians can eliminate the use of fluorescein completely, providing a noninvasive break-up time (NIBUT) value (*Figure 3*). Clinicians can perform this test by projecting concentric rings (using a topographer) on the cornea and evaluating the time

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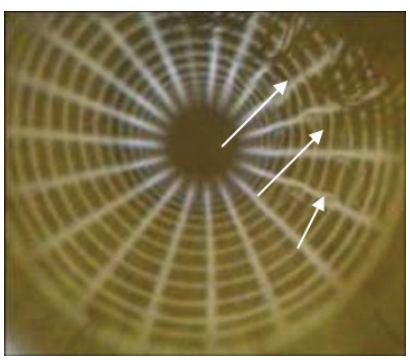

Fig. 3. This image depicts NIBUT, where the arrows indicate the areas of tear break up.

Photo: CORE

Fig. 4. Tear collection for osmolarity measurement using Tearlab.

taken for distortions of the rings to occur. Moreover, ideal NIBUT measurements should avoid any form of tear film additives by controlling the examination environment (no additional sources of heat, air movement or humidity, for example) and adopting a standardized head posture and blink behavior.

Tear evaporation rate is considered a potential indicator of tear lipid layer stability, as increased tear evaporation rates are associated with increased tear thinning, ocular dryness and discomfort.[34-37] Because of this, research suggests inter-blink tear evaporation may contribute to dry eye. Since no commercially available instrument exists, researchers have custom-built or modified instruments to determine tear evaporation rates.

Tear film osmolarity is a newer measurement that can provide insight into the balance between tear production, evaporation, drainage and absorption.[38] The osmolarity of the normal tear film is determined by the concentration of electrolytes in the mucoaqueous layer. Historically, tear osmolarity was measured using freezing point depression or vapor pressure osmometry; however, their clinical utility was limited.[39,40]

With the introduction of a new osmometer (TearLab), clinical evaluation of tear osmolarity has increased significantly (*Figure 4*). This instrument uses a 50nL tear sample to analyze the electrical impedance. Mean tear film osmolarity values in normal participants range between 270mOsm/L and 315mOsm/L, with an overall average of 300mOsm/L.[41-43]

Although the current method of tear collection involves collecting tears from the lower meniscus, clinicians should remember that the osmolarity across the ocular surface is different to that measured in the tear meniscus.[44] Further studies are warranted to help establish consistent cut-off values for DED, achieved by studying a cohort where osmolarity is not a diagnostic criterion and where the sensitivity and specificity are tested in an independent study population.

Researchers have also proposed tear ferning pattern assessment as a simple and economical test for dry eye diagnosis.[42,45,46] In this procedure, 1µl to 4µl of tears is placed on a glass slide, allowed to dry at room temperature (20°C to 26°C) and humidity (<50%). This slide is then observed using white light microscopy and photos are taken within 10 to 15 minutes.

In normal individuals, ferning patterns appear dense and uniform with closely branching ferns (*Figure 5*). However, they change with altered tear functionality and chemical composition; for example, in dry eye tears, ferning is less regular, with increased space between ferns and fern shortening, culminating in an absence of ferning altogether. Research shows tear ferning patterns are independent of sex, hormonal fluctuations in women with normal menstrual cycles and time of day during waking.[2]

When a tear function abnormality exists, the tear ferning patterns degrade, creating altered patterns

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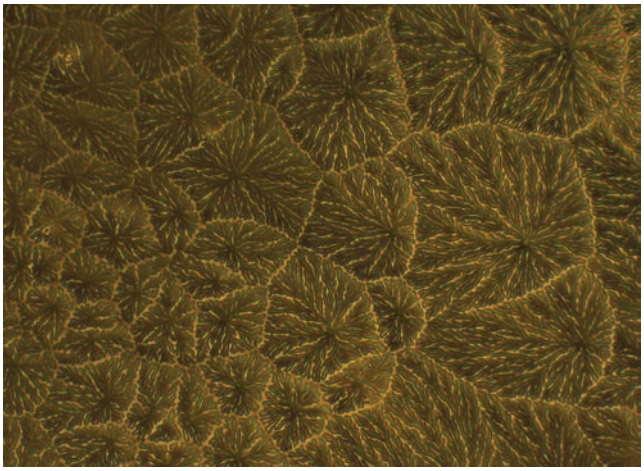

Fig. 5. This image illustrates the tear fern pattern in a normal individual.

seen in contact lens wearers and with increasing age, independent of dry eye status. Despite these promising results, more studies are needed to establish sensitivity, specificity and cut-off values in various forms of dry eye before this method can be adopted by clinicians on a regular basis.

The tear film is immensely important for the maintenance of a healthy ocular surface, and many changes occur to both the biochemical and biophysical properties of the tear film in DED. While further work will help us better characterize the biochemistry of the tear film and the role of tear film osmolarity, inflammatory markers and other biophysical properties over the entire ocular surface, much can be done now for patients. With the right knowledge and diagnostic tools, clinicians can monitor tear film changes that are harbingers of DED and initiate or alter treatment to help bring patients the stable tear film they need. RCCL

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Coping with Contact Lens Discomfort

Lens material and solution choices are part of the equation, but there is more to be considered. Here's how TFOS DEWS II can help.

By Lyndon Jones, PhD

Over the last two decades, a substantial number of new contact lens (CL) materials and lens care solutions have come onto the market. Despite these advancements, symptoms of discomfort and dryness persist in lens wearers, particularly at the end of the day. Studies estimate that 50% of all lens wearers continue to complain of dryness and discomfort at the end of the day, and 25% to 30% of all wearers will cease lens wear at some point, either temporarily or permanently.[1-4]

To address the issue of contact lens discomfort (CLD), in 2013 the Tear Film and Ocular Surface Society (TFOS) published a series of papers to better understand CLD and determine factors that may help alleviate its negative effects. Among the topics discussed in the report is the impact of CL materials, care systems and design on CLD.[5] For most practitioners, addressing lens material and solution choices for CLD patients may seem like an obvious way to help. Many studies show this can be beneficial and provide a solution to the associated discomfort and, in many cases, reduced wearing time. However, to effectively manage CLD, there is another factor that must always be considered—the patient.[6,7] It is important to remember that even the best material-solution combination will not work well if the patient's ocular surface is compromised.

Some potential patient and ocular surface factors associated with CLD include: female sex, younger age, poor tear film quality and quantity, seasonal allergies, systemic medications such as oral contraceptives and isotretinoin, diet, hydration, alcohol use, smoking, compliance with lens replacement and care systems and bulbar conjunctival and corneal staining.[4,6,7]

Last summer, TFOS introduced their second Dry Eye Workshop (DEWS II) report. While the report discusses dry eye disease (DED) in non-contact lens wearers, its management and therapy section can help practitioners better manage CL patients who remain symptomatic despite lens material and care system optimization.[5]

Here are some key takeaways from DEWS II that can guide our CLD management in clinical practice, as well as some evidence-based pearls not included in DEWS II.

OCULAR LUBRICANTS

CL wear rapidly destabilizes the already thin tear film. A typical CL is around 100µm thick, while the average tear film is 5µm to 7µm thick. As such, contact lens wear causes a rapid tear film break-up that typically occurs after six to seven seconds, at best, over the lens. In symptomatic CL wearers, the break-up is often even more rapid.[8,9]

The DEWS II management and therapy report covers many different formulations of ocular lubricants.[5] While many are not indicated for use with CLs *in situ*, they can be used pre- and post-lens insertion to improve the ocular surface and enhance the tear film.[10]

In another study, use of a microemulsion of mineral oil and a polar phospholipid surfactant as a CL rewetting agent over the lens resulted in improved comfort, reduced corneal staining and reduced lid wiper epitheliopathy.[11] The pre-application of a lubricant containing carboxymethylcellulose (CMC) can reduce solution-induced corneal staining, and a CMC-based lubricant can improve the initial comfort of a daily disposable CL compared

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with application directly from the blister-pack.[12,13] Thus, it appears that the concomitant use of lubricants (typically instilled pre-lens insertion and post-lens removal) can be beneficial in managing various complications associated with CL wear.

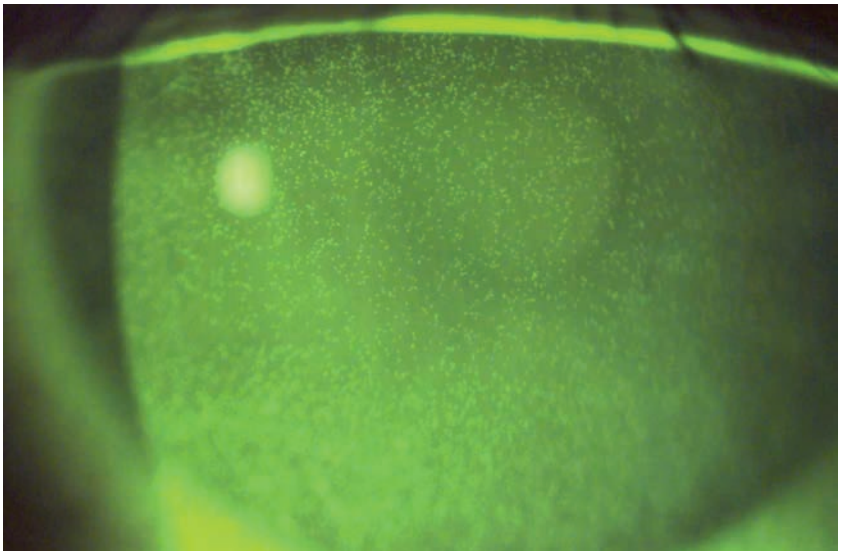
One key point to remember when applying topical drops with contact lenses is that the latter take up any preservatives, so any drops containing benzalkonium chloride should be avoided.[14] Drops that are preserved with newer, high molecular weight preservatives and oxidative preservatives are safe to use with soft lenses, and if concerns arise, using the drops with daily disposable lenses will limit lens uptake and release.

PUNCTAL OCCLUSION

This therapeutic approach, particularly in conjunction with other therapies, is valuable in the management of DED in non-lens wearers.[5] However, relatively few studies investigate the impact of punctal occlusion on CLD and in those few studies, the data is somewhat equivocal, suggesting that there may be better options to improve CLD than plugging the puncta.[15-17]

LID HYGIENE

It has been well established that lid conditions such as blepharitis and the overabundance of *Demodex* impact the ocular surface. The tear film changes that occur with these conditions will inevitably impact CL wearers and likely result in CLD. However, while many studies investigate the impact of lid hygiene on improving symptoms and signs of DED in non-lens wearers, little research exists on the impact of blepharitis or *Demodex* management in improving symptoms of discomfort in CL wearers. Of note, some studies suggest that the presence of *Demodex* is greater in CL wearers, symptomatic CL wearers have more demodex and the presence of *Demodex* results in a greater chance of CL dropout and discontinuation.[18-20] Given these points, management of both blepharitis and *Demodex* in CL wearers would be appropriate. Options here include lid hygiene wipes, topical antibiotics, topical ivermectin cream, oral ivermectin and various tea-tree oil preparations.[5,21]



Here is an example of solution-induced corneal staining. This can be reduced by pre-application of a CMC-based artificial lubricant.

MEIBOMIAN GLAND DYSFUNCTION

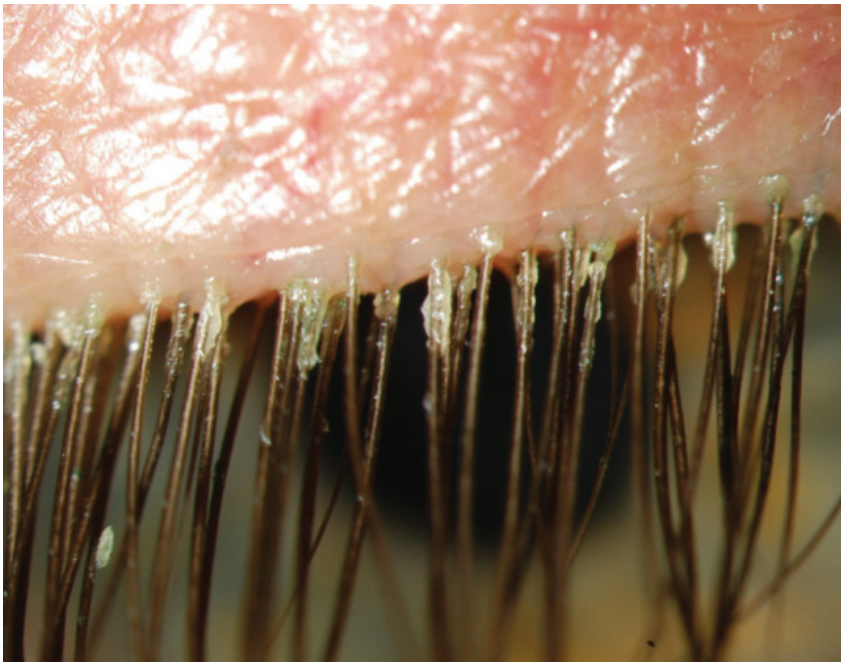
The association between CLD and meibomian gland dysfunction (MGD) is well known, and the positive impact of MGD treatment on improved comfort in CL wearers was first demonstrated more than 30 years ago.[22] Additionally, several studies have proposed that CL wear results in increased MGD prevalence.[23-26] As such, practitioners should carefully evaluate patients with CLD for MGD. If it turns out a patient does have MGD, a suitable treatment plan should be initiated.

Mechanical cleaning of the meibomian glands in cases of MGD includes forceful expression with or without heat, physical expression with heat using in-office devices such as LipiFlow (Tear Science), intense pulsed light (IPL), intraductal probing and debridement scaling of the lid margin.[5] A recent paper demonstrated an increase in mean comfortable CL wear time of approximately four hours per day in patients with MGD with a single vectored thermal pulsation treatment.[34] The most widely prescribed form of MGD management includes the application of warm compresses to the lids. However, studies show a wide variety of methods to apply heat to the eyelids, with no standard method recommended.[27-31] Because the methods used vary markedly in temperature achieved, care needs to be taken to ensure that the lids are appropriately warmed

to obtain a therapeutic effect of >40°C.[31-33] While several studies demonstrate the benefits of IPL, lid margin debridement scaling and device-assisted heating of the lids in the management of DED, to date there is a significant lack of studies investigating their use in the management of CLD, and more research is needed on this concept.[5]

ANTI-INFLAMMATORIES

Many studies confirm that DED is associated with an inflammatory process on the ocular surface, as evidenced by several review papers and acknowledged in the most recent DEWS II definition of DED.[35-40] Of note, one study proposes that CL wear actually induces a low-grade inflammation through the presence of the lens.[41] The management and therapy report describes several ways to manage this localized inflammation, including a wide variety of topical and systemic medications.[5] While the use of multiple types of anti-inflammatory drugs are reported in the management of corneal infiltrates, microbial keratitis, corneal abrasions and various types of ocular surface disease and in cases of CL-induced disease (sometimes with the concurrent use of bandage lenses), few studies have been published that have investigated the impact of anti-inflammatory drugs on CLD. The use of cyclosporine 0.05% emulsion in the management of CLD was proven to be successful in one study but ineffective in another.[42,43] One study did show that a four-week treatment with topical azithromycin ophthalmic solution was well tolerated and resulted in a significant improvement in comfortable CL wear time in patients with CLD.[44]



***Demodex* blepharitis in a rigid gas permeable contact lens wearer suffering from long-term discomfort.**

DIETARY MODIFICATIONS

Much data now exists on the role of increased water intake, reduced caffeine and other dietary modifications that can impact DED.[5] Of these, the greatest amount of data exists on the beneficial role of essential fatty acids, most notably the appropriate balance of omega-3 and omega-6 intake.[5,38,45-49] Essential fatty acids have a broad range of systemic anti-inflammatory effects, including inhibiting the production of several pro-inflammatory cytokines—such as interleukin (IL)-1, IL-2 and tumor necrosis factor alpha—and preventing T-lymphocyte proliferation, which have been implicated in the pathogenesis of DED.[5] In addition, they have beneficial effects on meibomian gland lipids.[5,50] Several studies have demonstrated the benefit of appropriate dietary supplement intake on enhancing CL comfort in patients with dryness symptoms.[51-54]

The TFOS DEWS II management and therapy report makes it clear that management of ocular surface disease is of great value in the battle to reduce symptoms and signs of CLD. As such, practitioners need to look beyond lens material and care regimen. A careful assessment of the ocular surface could lead to increased CL success and reduced CL dropout rates. RCCL

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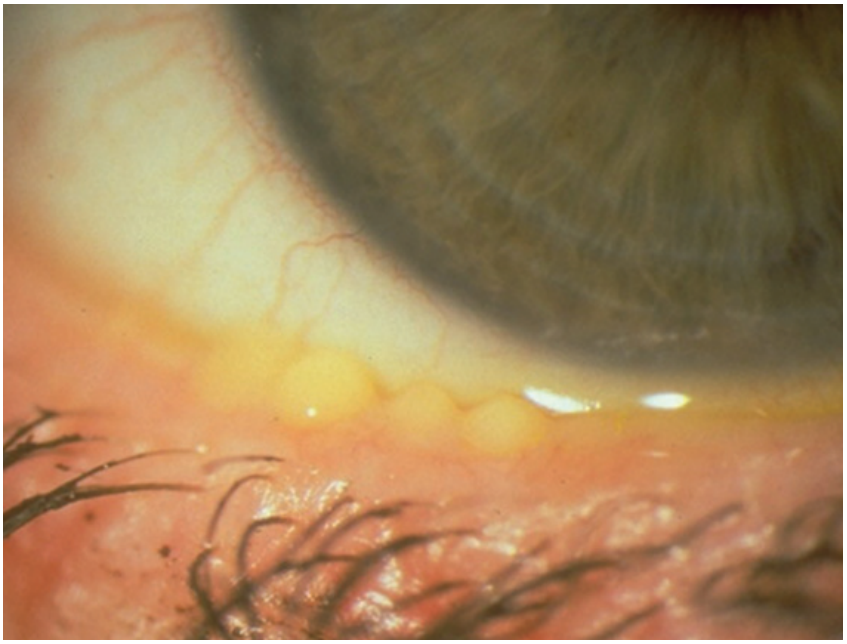


MGD in a contact lens wearer with reduced CL comfort.

LOOK OUT FOR IATROGENIC DRY EYE

Surgery, medications and contact lenses are just some of the ways a doctor's care can induce DED. Here's what DEWS II recommends to prevent it.

By Michael Iannucci, Associate Editor

A notable addition to TFOS DEWS II is a report on iatrogenic dry eye. Not a subject covered in the original DEWS report, it was time to acknowledge "the number of cases of dry eye that are caused by medical examination or treatment such as topical medications, systemic drugs, ophthalmic surgical procedures and even cosmetic procedures," says James S. Wolffsohn, PhD, a member of the DEWS II iatrogenic subcommittee and harmonizer for the report.

The goals of the subcommittee included the development of a classification system to help identify iatrogenic causes of dry eye as well as prophylaxis and management recommendations. To get there, they first had to define iatrogenic dry eye, which led to a consensus of "dry eye induced unintentionally by medical treatment from a physician or a health-related professional," Subcommittee Chair José Alvaro Gomes, MD, said during the 2017 ARVO session in which the report was introduced.

The subsequent classification system covered the following categories: ophthalmic surgery, pharmaceuticals, contact lenses (CLs), non-surgical ophthalmic procedures and non-ophthalmic conditions.[1]

This article discusses the new findings in iatrogenic dry eye and how you can use them to better serve your patients.

PROCEDURES

Findings in surgery-induced dry eye are among the most revealing of the report. The subcommittee looked closely at the literature on refractive, cataract, lid, conjunctival, glaucoma, vitreoretinal and strabismus surgeries, as well as keratoprosthesis, intrastromal corneal ring segment implantation.

Refractive Surgery. The research on dry eye symptoms after laser-assisted *in situ* keratomileusis (LASIK) reveals a wide range of incidence statistics based on factors such as the severity cut-off and whether the patient had pre-existing dry eye disease (DED).[2-11] Some studies suggest that photorefractive keratectomy (PRK) induces fewer dry eye symptoms than LASIK because it only damages corneal nerve endings, resulting in faster regeneration.[12,13] The subcommittee is quick to point out, however, that it is unclear "whether there is retrograde degeneration of nerves following terminal injury in the cornea."[1]

Photo: Derek N. Cunningham, OD, and Walter O. Whitley, OD, MBA

During LASIK flap creation, corneal nerves are severed, which can induce dry eye.

Prior to surgery, the most common cause of dry eye is obstructive meibomian gland dysfunction (MGD).[14-16] After the procedure, dry eye causes include the effects of neurotrophic influences on the lacrimal functional unit.[17]

To best manage dry eye in refractive surgery patients, the subcommittee recommends treating pre-existing DED, ocular rosacea or blepharitis before surgery. Restasis (cyclosporin A, Allergan) is an effective treatment in some cases, but adjuvant options include nonpreserved artificial tears and ointments, dietary alpha omega fatty acids, maintaining more than 40% to 50% humidity, punctal plugs and even autologous serum drops.[18] In general, clinicians should continue the selected course of treatment for six to eight months after surgery.[19]

Cataract Surgery. Although the majority of these patients are older (between 43 to 84 years of age according to one study) and more likely to have pre-existing DED, the surgery itself may temporarily induce or exacerbate dry eye on its own.[20-25] Of note, diabetes patients show an increased vulnerability to dry eye after undergoing cataract surgery.[26,27] Potential contributors to cataract surgery-induced dry eye include topical anesthetics and desiccation, nerve transection, elevation of inflammatory factors, goblet cell loss and MGD.[28]

As with refractive surgery, management of these cases begins with identifying and treating ocular rosacea, blepharitis and ocular surface disease prior to surgery.[29-31] Here, however, clinicians should avoid lid hygiene treatments shortly before or after surgery to avoid any infectious complications.[1] "Care should be taken to avoid lid hygiene immediately prior to, or shortly after, the surgery, as the eyelids harbor pathogens that could be introduced to the ocular surface, increasing the risk of infections such as endophthalmitis when the cornea is compromised through an incision to implant an intraocular lens," says Dr. Wolffsohn.

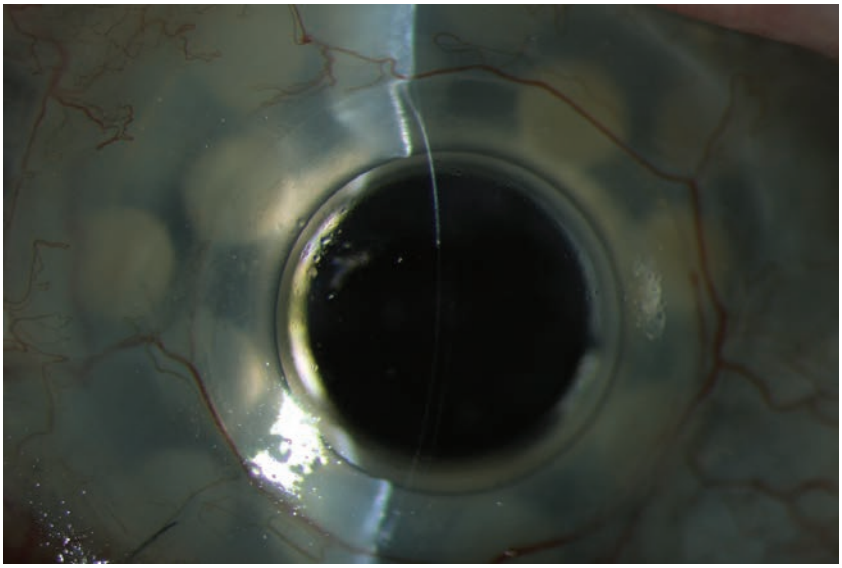


Photo: James Aquavella, MD

Studies have shown that reorganization of the nerves after keratoprosthesis implant is a possible cause of DED.

The subcommittee recommends using medical therapy or artificial tears that include hyaluronate or carboxymethylcellulose to improve dry eye signs and symptoms after cataract surgery.[32-36]

Lid Surgery. A close interaction of the eyelid, tear film and ocular surface could be a possible cause of dry eye in lid surgery patients.[37] These surgeries often cause DED onset or exacerbate preoperative disease, which, according to the report, is common but overlooked.[37-41] Management options include artificial tears and lubrication throughout the night (specifically, unpreserved products), topical steroids and Restasis.[40,41] In persistent cases, surgical intervention such as tape tarsorrhaphy and lower lid repositioning may be necessary. Here, the subcommittee recommends addressing ocular surface issues prior to surgery.

Other Surgeries. In keratoprosthesis implantation, post-procedure nerve reorganization surfaced as a possible culprit for dry eye (*Figure 3*). "It has been shown, for example, that following penetrating keratoplasty, central corneal sensitivity decreased and then returned to near normal levels after 12 months, but no sub-basal nerves were detected," says Dr. Wolffsohn. "Hence regeneration may not follow the initial structure, which has a negative effect on ocular surface simulation of the tear film components."

For conjunctival surgery, the subcommittee found a relationship between pterygium growths and DED, although it is still not entirely clear if the growths actually cause the disease.[42] Some other surgeries that showed links to dry eye without concrete causation include glaucoma surgery, vitreoretinal surgery, strabismus surgery and intrastromal corneal ring surgery.[1]

DRUG-INDUCED DRY EYE

This can be related to either topical or systemic medications:[1]

Topicals. The subcommittee found that the concentration of

preservatives in glaucoma medications, specifically benzalkonium chloride (BAK), has the potential to cause inflammation and proptosis. "Due to financial prudence, health services tend to initially prescribe preserved glaucoma medications, as they are generally less expensive," says Dr. Wolffsohn. "Preservatives damage the ocular surface and can exacerbate dry eye."

Additionally, investigators say a number of other topical drugs can "cause or aggravate" DED, but because they are commonly tested in preserved formulations, the respective roles of the drug, preservatives and excipients isn't exactly clear).[1]

To manage cases where topical drugs are the suspected dry eye culprit, ODs should discontinue the drug, if possible.[1] This becomes tricky if several drugs are being used at once or if discontinuation of the drug would endanger the patient's eye health. Eye drops can alleviate dry eye symptoms, and in severe cases, laser trabeculoplasty or surgery may be necessary. Alternatively, ODs could use low toxicity preservatives such as brimonidine to minimize the drug's toxicity.[43]

Systemics. Of the top 100 best-selling systemic drugs in the United States in 2009, 22 can possibly cause dry eye symptoms.[44] The DEWS II iatrogenic subcommittee compiled a lengthy list of systemic drugs with either a "known or suspected link to dry eye symptoms." These range from nonsteroidal anti-inflammatory drugs to multivitamins, and their associations with dry eye symptoms vary.[1]

To identify a problematic systemic drug in these cases, practitioners can often withdraw and then reintroduce the drug in question.[1] For cases in which discontinuation is not possible, options include adjusting the dosage to a point where the drug is still effective but with reduced dry eye symptoms, switching to a medication of a different mechanism or, in mild cases, adding lubricants or similar topical treatments.

CL-INDUCED DRY EYE

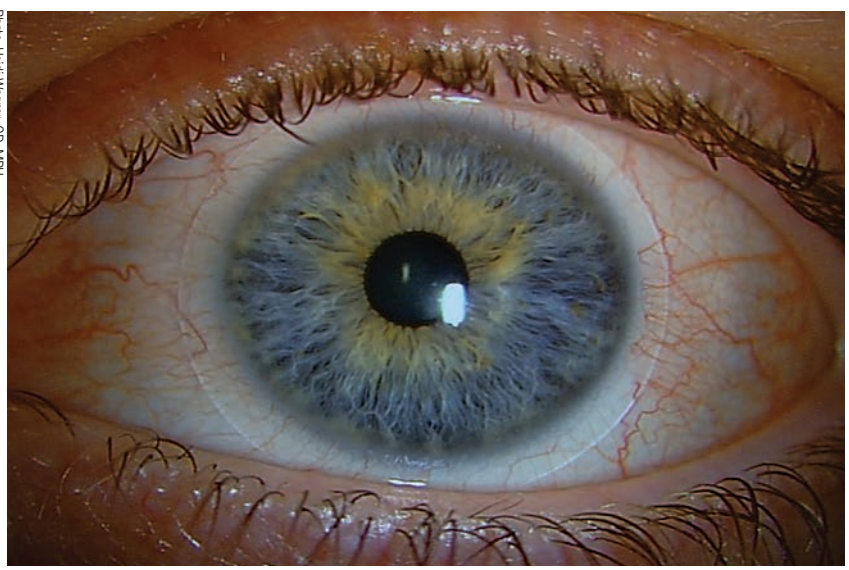
Factors involved in dry eye stemming from CL wear include biophysical changes to the tear film such as a thinner lipid layer and increased tear evaporation, and ocular responses such as alterations to Langerhans cells, conjunctival goblet cell density and lid wiper epitheliopathy. Of course, existing DED can be exacerbated by lens wear, and lenses can induce a dry eye state.[1]

The report also found evidence that CLs affect meibomian gland expressibility, the number of plugged and expressible orifices and gland-related dropout. "*In vivo* confocal microscopy of the meibomian glands shows significantly decreased basal epithelial cell density, lower acinar unity diameters, higher glandular orifices diameters and greater secretion reflectivity with contact lens wear," says Dr. Wolffsohn. "There is no evidence that these changes are reversible, so clinicians should make sure that contact lenses have minimal impact on the ocular surface to hopefully minimize changes to the meibomian glands."

When a patient has CL-induced dry eye, management options include switching to daily disposable lenses, introducing lenses with internal wetting agents, using topical wetting agents, hydroxypropyl cellulose ophthalmic inserts, hydrogen peroxide disinfection, omega-3 and omega-6 fatty acid supplementation, punctual plugs, azithromycin, reduced lens wear time and, if needed, discontinuation of lens wear.[1]

NONSURGICAL OPHTHALMIC PROCEDURES

Botox (botulinum toxin, Allergan), a neurotoxin used to treat various conditions such as blepharospasm, migraine and cervical dystonia, has emerged as a possible cause of DED.[1,45] Patients with dry eye symptoms after Botox treatment may experience relief with artificial tears;if symptoms persist after 12 months, surgical intervention such as lateral musculoplasty may be required.



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A hypersensitivity or toxic reaction to the preservative in a contact lens solution can cause dry eye symptoms and is typically characterized by conjunctival injection and superficial punctate keratitis.

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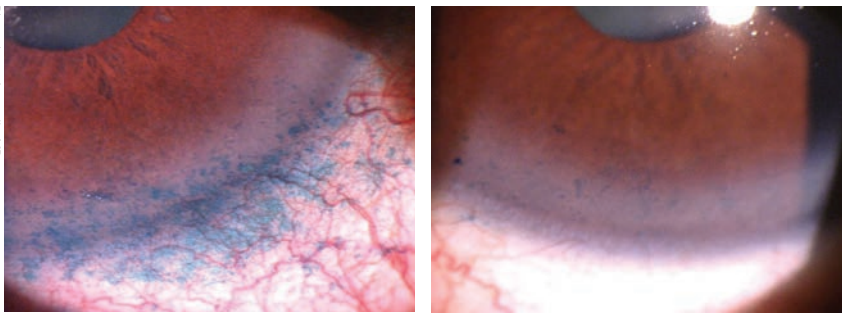

Lissamine green staining of the conjunctiva and cornea identifies BAK toxicity from chronic prostaglandin use. This patient was switched to a preservative-free prostaglandin analog. His signs and symptoms of dry eye improved over the next three months.

Other nonsurgical ophthalmic procedures that show a lesser degree of dry eye prevalence include corneal collagen crosslinking, positive pressure noninvasive ventilation, radiation treatment, eye makeup, tattooing and piercing.[1]

The past 10 years of research shows that the inclusion of iatrogenic dry eye in DEWS II was necessary, and the results will help practitioners better handle ambiguous DED. The report "drills down into the specifics of each treatment or condition of a patient," says Dr. Wolffsohn, "so it really provides clinicians with a useful guide to some of the key areas they need to concentrate on in patient history and symptoms." RCCL

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By Robert Ensley, OD, and Heidi Miller, OD

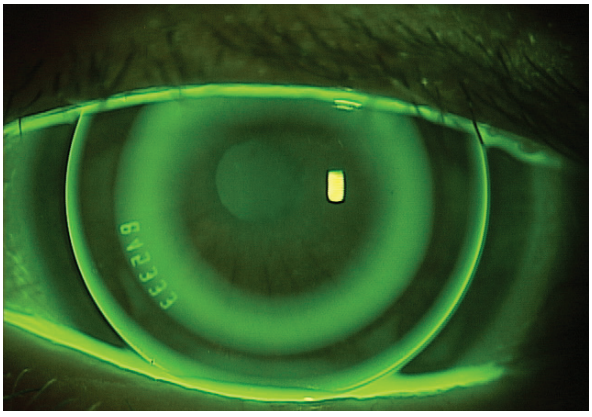
CLD? Consider Ortho-K

An unusual suggestion, but it may work for some patients with contact lens discomfort.

Several years before the release of the Tear Film and Ocular Surface Society's (TFOS) Dry Eye Workshop II report, TFOS conducted a separate workshop investigating contact lens discomfort (CLD). Defined as "a condition characterized by episodic or persistent adverse ocular sensations related to lens wear," CLD can lead to reduced wearing time and eventual discontinuation.[1]

When patients begin complaining of discomfort, contact lens wear and a multitude of environmental factors may confound the practitioner's assessment and management strategy for CLD. However, in the absence of evident ocular surface disease, the primary focus is often placed on the contact lens choice. To combat CLD, the most common initial steps include changing contact lens materials, care systems and increasing the lens replacement frequency to a daily disposable modality.

Although seldom considered, orthokeratology (ortho-K) is another viable option to prevent discomfort and subsequent discontinuation of contact lens wear.



Ortho-K can be a unique option for some patients strugging with contact lens-related discomfort.

WHY ORTHO-K?

The origins of this modality, also called corneal reshaping or vision shaping treatment, date back to George Jessen's orthofocus technique in which polymethyl methacrylate lenses were intentionally fit flatter than the corneal curvature to mold the cornea and reduce myopic levels.[2] Modern ortho-K lenses now use higher dK gas permeable materials with a reverse geometry design to reshape the anterior cornea. Worn in a closed-eye setting while the patient is asleep, these lenses often temporarily correct refractive error after lens removal.

It seems obvious that ortho-K, which eliminates the need for contact lens wear during waking hours, would effectively mitigate CLD. Several studies have compared the performance of ortho-K with daily soft contact lens (SCL) wear. One early study in 2005 compared ortho-K with hydrogel SCLs and found 67.7% of participants preferring ortho-K to SCLs. When asked about symptoms such as itching, dryness or lens awareness in each modality, ortho-K lenses rated better, even with some patients who preferred SCL wear.[3] A similar study using the National Eye Institute Refractive Quality of Life questionnaire also demonstrated decreased ocular symptoms and perceived visual independence with ortho-K wear.[4]

A decade later, researchers more specifically compared dry eye symptoms between ortho-K lenses and newer generation silicone hydrogel (SiHy) SCLs. In one study, both habitual SiHy wearers and neophyte contact lens wearers were fit in ortho-K lenses. Several dry eye indices, including Ocular Surface Disease Index (OSDI), tear breakup time and goblet cell density (GCD), were recorded at baseline and after one month of lens wear. For previous SiHy wearers, the OSDI score improved and GCD increased after only one month of ortho-K lens wear.[5]

A second study compared both signs and symptoms of ocular dryness between SiHy and ortho-K lens wearers over the course of

NEW MODALITY, NEW RISKS

While ortho-K eliminates CLD during waking hours, it comes with its own risks. Proper patient education can go a long way to reduce even these potential problems. Corneal edema and staining are two of the most common side effects, and researchers have noted others such as pain, redness, tearing, irritation, discharge, ocular abrasion or visual distortion.[1-3]

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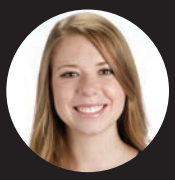

three months. To assess subjective symptoms, researchers used a dry eye questionnaire to elicit symptoms such as dryness and discomfort. Biomicroscopy helped to evaluate bulbar and limbal redness and conjunctival staining. The results showed that end-of-day discomfort and dryness in the ortho-K group were lower than the SiHy SCL group, with the higher levels of discomfort corresponding to increased redness and conjunctival staining.[6]

HOW IT WORKS

In 2002, the Food and Drug Administration approved the first overnight ortho-K lens for the treatment of up to -6.00D of myopia, with or without -1.75D of astigmatism.[7] While treatment of low to moderate myopia under -4.00D has a higher rate of success, the off-label treatment of more than -6.00D can be successful.[8]

The original theory, based on Jessen's orthofocus technique, was the entire cornea would bend and flatten from lens compression.[2] Topographical analysis of ortho-K wear does show flattening of the central treatment zone; however, more current research suggests anterior corneal tissue is redistributed with the help of tear film forces.[9] The exact mechanism is still debated, but histological studies using a feline model have shown both corneal epithelial cells and anterior stroma undergo change.[10,11] As a result, corneal thickness measurements confirm the thinning of the central cornea while the mid-peripheral cornea thickens.[9,12]

Although widely used for myopia, ortho-K lenses can also be used to treat low levels of hyperopia. Similar to the mechanism for myopia reduction, tear film forces are thought to be involved with corneal reshaping. By fitting the lens steep, the post-lens tear film supposedly creates a suction force inducing central corneal steepening.[13] Studies have indicated close to a 1D refractive shift can be expected after one night of wear as a result of central corneal steepening and mid-peripheral flattening.[13,14] However, the use of fenestrated lenses without a statistical difference in clinical effect suggests the tear film forces are more likely a compressive force than a suction force.

Ortho-K has maintained popularity thanks to its role in myopia control for children.[15] The ability to correct refractive error at night—eliminating the need for daytime lens wear—makes these lenses a great option for patients with low hyperopia and mild presbyopia as well. If patients have struggled with CLD but aren't fond of spectacle wear, ortho-K may be a viable option if they fall within correctable parameters. RCCL

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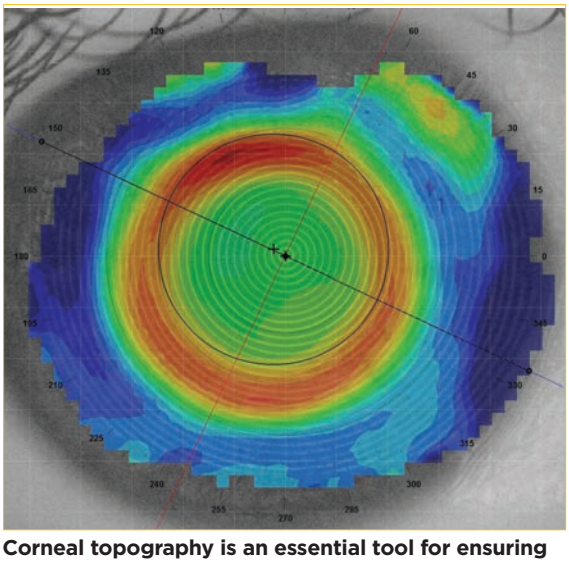


Corneal topography is an essential tool for ensuring proper centration of an ortho-k lens.

By Vivian P. Shibayama, OD

Double Trouble in Keratoconus

Lenticular astigmatism complicated an already-difficult case. This patient needed a little extra help before finding a good fit.

Typically, patients with significant lenticular astigmatism are not the best candidates for non-toric rigid gas permeable lenses (RGPs).[1] However, RGPs *are* often ideal for patients with keratoconus—leaving the clinician with some tough decisions when it comes to fitting contact lenses for patients with both conditions. A recent keratoconus patient with significant lenticular astigmatism highlights the challenges—and the rewards—of working through the problem with the patient and fellow clinicians.

THE CASE

A 69-year-old male with keratoconus presented with complaints that his glasses, fit four weeks prior, were not working for him. He said he felt a pulling sensation while wearing the glasses and his vision was blurry. He stated that he would like to avoid contact lenses due to past issues with insertion and removal.

His presenting prescription was -2.25 +6.75x001 OD and -0.25 +4.00x011 OS. Visual acuities (VAs) were 20/30- OD and 20/25+ OS. A manifest refraction of +0.75 +4.25x005 provided a VA of 20/20- OD, while -3.75 +8.00x003 gave him a VA of 20/25+ OS. The prescription was trial framed on the patient, and although his vision was clearer, he said the prescription gave him diplopia at both distance and near, making mobility difficult.

Slit lamp exam revealed 1+ inspissated meibomian glands and central corneal thinning OU, while the anterior chamber was deep and quiet OU. The iris was normal with 1+ nuclear sclerosis OU. Intraocular pressures were 12mm Hg OD and 11mm Hg OS. Topographical imaging revealed central corneal steepening of 51.37/47.2D OD and 48.01/43.95D OS (*Figure 1*).

After a long discussion of the corrective options, the patient decided to try contact lenses again, given the glasses provided no improvement.

INITIAL FIT

Due to the inferior broadness of the cone, I started the diagnostic fitting with large-diameter intralimbal RGPs. A 7.34 base curve (BC)/-6.00/11.2 diameter lens was placed on the patient's right eye. Although the central fit was slightly flat and the peripheral edge had insufficient edge clearance, the lens exhibited good movement and centration.

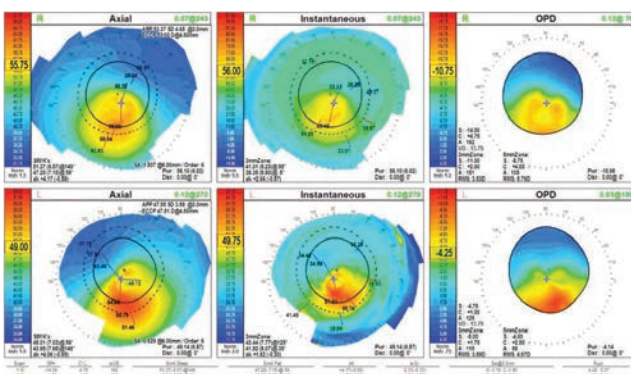


Fig. 1. The patient's corneal topography shows that the inferior central cones are steeper OD than OS.

A spherical over-refraction of +1.50 caused monocular blur and vision of 20/50. Cylindrical over-refraction of -1.25 +2.75x078 provided a VA of 20/25 with no distortion.

For the left eye, I chose a 7.42/-6.00/11.2 lens. On eye, it exhibited light apical touch, an aligned peripheral edge, and was well centered with good movement. The over-refraction was +2.50 20/25-, and the patient complained of blur. The vision cleared with a plano +1.75x120 20/25 sphero-cylindrical over-refraction. The prescription was placed in trial frame over the contact lenses and the patient felt comfortable and his vision was clear. Autokeratometry was performed over the RGPs to determine if the lenses were flexing, which could also be a cause of residual astigmatism. No flexure was noted.

The right lens was slightly steepened to vault the cone, and the peripheral curves were widened and flattened. More minus power was added to compensate for the change in BC. The left lens parameters were kept the same as the diagnostic lens with the only change being the over-refraction. The following lens order was placed:

- OD: 7.11/-8.25/11.2; P1 0.4/9, P2 0.4/10.5, P3 0.4/10.5
- OS: 7.42/-6.00/11.2; P1 0.5/9, P2 0.5/11.75

A glasses prescription was also dispensed to be worn over the contact lenses to correct the residual astigmatism:

- OD: plano +2.75x075 (VA of 20/30)
- OS: plano +1.75x125 (VA of 20/25)

WEEK ONE

The patient presented for dispensing with no changes. He put the lenses on and reported immediate diplopia even with the spectacle correction. The patient was advised to wear the prescription for an hour a day to see if the diplopia would improve.

WEEK TWO

The following week, the patient presented with complaints that he could not adjust to the new prescription, even after wearing the combination one hour a day. His vision was blurry without the glasses over the contacts, and the glasses gave him double vision. The patient was referred to his cornea specialist for a cataract consult, in the hopes that removing the right eye cataract would eliminate the lenticular astigmatism and the need for glasses to correct the residual astigmatism.

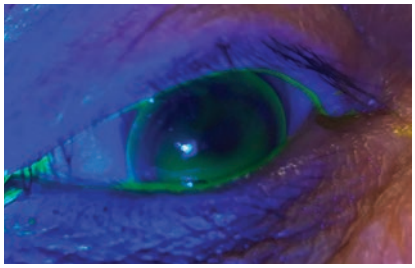
POST-PROCEDURE

The surgeon agreed with the plan and performed the operation one month later. The surgeon placed a spherical intraocular lens in the patient's right eye. The patient presented two weeks after surgery to take measurements for a lens OD. A 7.34/-6.00/11.2 diagnostic lens was placed on the patient's right eye. The over-refraction was +10.50 sphere, bringing the patient to 20/20.

The left eye corrected to 20/25- with a spherical over-refraction. The patient had slight double vision with this lens, but we decided to not prescribe glasses to correct the residual cylinder in his left eye because of his past intolerance.

The following lenses were ordered with the right lens adjusted slightly steeper to vault the cone:

- OD: 7.11/+4.50/11.2; P1 0.4/9, P2 0.4/10.5, P3 0.4/10.5
- OS: 7.42/-2.25/11.2; P1 0.5/9, P2 0.5/11.75



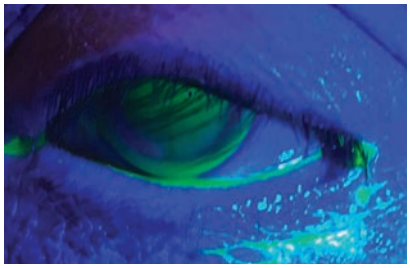


Fig. 2. These images show the RGP lenses on the right and left eyes. You will note the good centration with light apical touch.

FINAL FOLLOW UP

The patient returned for his dispensing appointment, and once the lenses were inserted, he reported no binocular diplopia. Vision was 20/20 OD, 20/25- OS. The lenses exhibited light apical touch OU with good centration and movement. The patient was sent home to try the lenses with +2.50 readers.

He returned one week later with a positive report. His vision was slightly doubled in the left eye when he covered one eye, but he didn't notice it when both eyes were open. He was quite happy with the final contact lens prescription and the vision it provided.

DISCUSSION

Residual astigmatism is defined as the astigmatic refractive error still present after a lens is placed on the cornea.[2-4] This can be very difficult to manage in patients with keratoconus. It often precludes patients from wearing RGPs; yet, soft lenses may not mask the irregular corneal astigmatism in patients with keratoconus. In this case, removing the lenticular astigmatism by way of lens replacement led to a successful outcome. If the residual astigmatism was still present after cataract surgery, the surgeon had plans to replace the cornea.

Finding the source of the residual astigmatism is the key to management. Autokeratometry or topography should be performed over the contact lenses to determine if the cylinder is induced by lens flexure. If the residual astigmatism is truly physiological, it can be corrected by spectacles or contact lenses that incorporate front surface astigmatism.

In addition, rotational stability is often a challenge when fitting RGPs. In cases where front surface toric RGPs and spectacles fail, cataract surgery can often address lenticular astigmatism, such as in this case. RCCL

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MK: A Stealthy Opponent

Differentiating microbial keratitis isn't always cut-and-dry. These tips can help.

Microbial keratitis (MK), including bacterial, fungal and protozoan forms, is a common clinical entity, with an estimated 30,000 to 70,000 cases each year in the United States.[1,2] Though medical management is often successful, these pathologies continue to be a significant source of corneal vision loss, emergent keratoplasty (in cases of impending infectious perforation), non-emergent keratoplasty (to treat resultant scars) and, rarely, enucleation or evisceration.

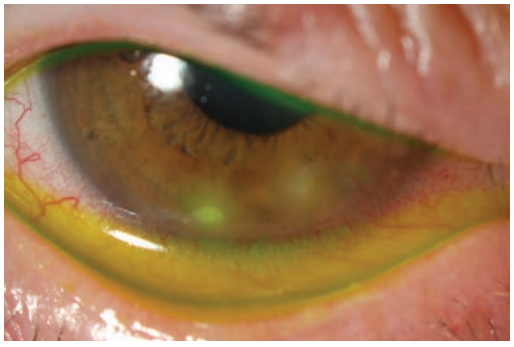
Infectious corneal ulcers don't always make their intentions known on presentation and their care, no matter how insignificant the original ulcer, needs to be carefully managed to ensure the best outcome.

The first, often trivialized, step in managing an infectious corneal ulcer is defining the lesion as microbial in nature. This is a question everyone struggles with on occasion. Many cases of MK will be easily discernible from other pathologies, but not all of them. Everything from corneal deposits and inflammation to edema may occasionally masquerade as a possible infection.

Let's take a closer look at the various management aspects of MK, beginning with differentiation. Subsequent columns will walk you through when to culture, common treatment strategies, the role of emerging resistance in treatment and advanced treatment options.

THE DIFFERENTIALS

As the name implies, an infectious corneal ulcer almost universally requires an epithelial ulceration. Exceptions to this rule are rare and include early-stage *Acanthamoeba* epithelial keratitis (AK) and some fungal infections that may be so indolent the epithelium heals over them. But for the most part, microbial pathogens require a breach in the epithelium to adhere to and colonize the cornea. Because the resultant inflammation will prevent migration of the epithelium over the top—stromal inflammation impedes epithelialization—MK should have an epithelial defect as large as or larger than the infiltrate. Of course, most epithelial defects are not infectious in origin, and for the cause of a defect to be MK, an infiltrate must be present at its base.



Sterile marginal keratitis is differentiated easily from microbial keratitis based on location. This patient had no specific risk factors for microbial keratitis.

MK infiltrates are generally grey, white or yellow, quite dense, typically (though not always) round or oval and well circumscribed (unlike zones of corneal edema, which have more nebulous margins).

Other non-infectious sources of corneal infiltration include hypersensitivity reactions, contact lens keratitides and stromal viral keratitis. These may result in an infiltrated stroma, though they are often multifocal, small in size or may not have an epithelial ulceration. To differentiate, the size of the lesion is key, as those with diameters 2mm or greater are typically infectious. Extracorneal signs can be helpful, with mucous discharge and heavy anterior chamber reaction being more common in microbial cases compared with serous discharge and little to no anterior chamber reaction in non-microbial cases.

Location should also play a prominent role in your differential. Due to differing zones of corneal immunity (with the peripheral cornea being immediately adjacent to the immunologically active limbal zone and the central and paracentral cornea being immune privileged) the cornea will respond variably depending on the location of the insult. The peripheral cornea is more likely to contain MK in its cradle, but also more likely to generate hypersensitivity reactions. The central cornea is less likely to generate hypersensitivity reactions, but isolated lesions of this zone are more likely to be infectious (including viral etiology) rather than sterile. While not all lesions of the periphery are sterile and not all central infiltrates are infectious, lesion location should weigh into your final differential.

The final element in differentiating the likelihood of MK from other forms of keratitis is a careful patient history. This is crucial to uncovering a historic risk that supports the development of MK. Roughly 90%

of MK cases have a historic risk factor that compromised the cornea, allowing adherence of the microbe and subsequent colonization.[3]

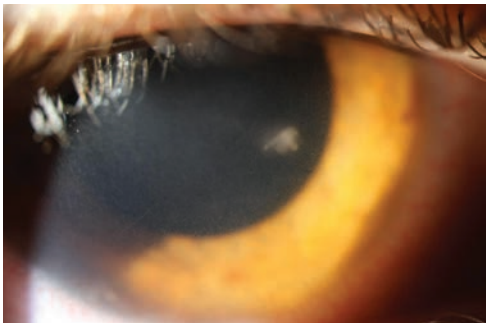
For those without a risk factor, other possibilities such as viral keratitis should be considered more closely. Further, the specific risk factor should also influence your diagnosis. Patients with contact lens use can have gram-positive, fungal or protozoan etiologies, though gram-negative species become relatively more common in this setting. Patients with chronic ocular surface disease or ophthalmic surgery as a risk factor likely have a normal flora etiology, often Staphylococcal. Finally, when patients present with a history of environmental trauma, the index of suspicion should tilt dramatically towards atypical bacteria and fungi.

SPLITTING HAIRS

Once you know you are dealing with MK, you should further differentiate the offending agent: gram-positive, gram-negative, atypical bacteria, fungus or *Acanthamoeba*. This will have dramatic bearing on whether you culture or not, and what initial therapy you select.

Though a definitive diagnosis is clinically impossible, given classic features are sometimes absent and individual immune differences create varying clinical appearances even among ulcers of the same species of bug, general trends can help you hone in on the right culprit and appropriate treatment. Gram-negative ulcers tend to have infiltrates with greater suppuration (more mucous-like in appearance) and may be less uniform in their density. When teaching, I tend to describe their density in culinary terms (chowder-like or like soft serve ice cream—disgusting, I know, but generally accurate). These ulcers also tend to worsen more rapidly, whereas gram-positive ulcers tend to progress more slowly (except *Streptococcus pneumoniae)*.

Gram-positive ulcers are often somewhat dry in appearance, tend to have less surrounding edema, are generally well-defined and uniform and will frequently display a prominent anterior chamber reaction.



This infiltrate is roughly the same size as those in the first image but, based on location, is most likely microbial in nature. While no definitive rule regarding location exists, a central ulcerated infiltrate larger than a pinhead has a high likelihood for being infectious in nature. When paired with other risk factors, such as contact lens use, suspicion goes up even higher.

Fungal ulcers are well known for their potential to form feathery infiltrates, be leathery in appearance, grow satellite lesions and, depending on the specific fungal etiology, generate a pigmented infiltrate. While these are all helpful indicators, one review found that more than 50% of fungal ulcers initially don't have any findings suggestive of a fungal etiology—a feature that leads to frequent initial misdiagnosis.[4]

AK in its early stage is an exception to the general rules of clinical appearance of corneal infection, as there is no well-demarcated infiltrate. Instead, early AK is characterized by a localized cystic epitheliopathy, which may be lightly infiltrated, but looks vastly different from its bacterial and fungal counterparts and is frequently confused with herpetic disease.[5] Perineuritis, which may be subtle or obvious, can further clue the clinician into an amoebic etiology. In its late stages, AK is characterized by a ring ulcer. This infiltrate has greatest density around its edges, is generally well centered around the corneal apex and is ulcerated (distinguishing it from the Wessely immune ring processes seen with viral eye disease and, occasionally, with gram-negative bacteria).

Once you know an infiltrate is infectious and the specific etiology you are likely dealing with, you are ready to use these diagnostic considerations to inform your treatment decisions—giving your patient the best possible outcome. RCCL

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By Christine W. Sindt, OD

Breaching the Border

HSV keratitis can allow limbal blood vessels to infiltrate the stroma, putting vision at risk.

A 47-year-old male presented with a red, irritated left eye one month after being fit in scleral lenses to address visual disturbances from post-LASIK ectasia. A short course of fluorometholone (FML, Allergan) QID quieted the eye, but it flared on several subsequent lens fits. He was diagnosed with herpes simplex virus (HSV) limbitis/stromal keratitis and started on FML and valacyclovir (Valtrex, GlaxoSmithKline), both BID.

Limbitis is an active epithelial or stromal HSV lesion occurring at the corneolimbal junction.[1] In epithelial disease, marginal lesions often are less dendritic in appearance than central ones, and proximity to blood vessels at the limbus allows white cell infiltration and neovascularization of the underlying corneal stroma. Stromal lesions do not usually occur concurrently with epithelial disease but may result from active viral infection or immune and inflammatory reactions. Immune (non-necrotizing) keratitis occurs in 20% to 60% of eyes with recurrent HSV keratitis and accounts for 90% of recurrent stromal keratitis.[2]

Blood vessels may grow into the normally avascular stroma, especially in long-standing disease, and may regress with treatment. Stromal scarring almost always results and can decrease vision significantly, depending on location and severity, requiring treatment of active inflammation. Stromal thinning, fibrosis, pannus and lipid deposits are common.[3]

At one-month follow up, the patient was refit into a corneal GP/daily disposable piggyback system and treatment tapered to QD as a maintenance dose. He has had no recurrence of disease; however, his ectasia has progressed. He will proceed with crosslinking but will increase his dosing of the prophylactic antiviral prior to the procedure and throughout the postoperative period. RCCL

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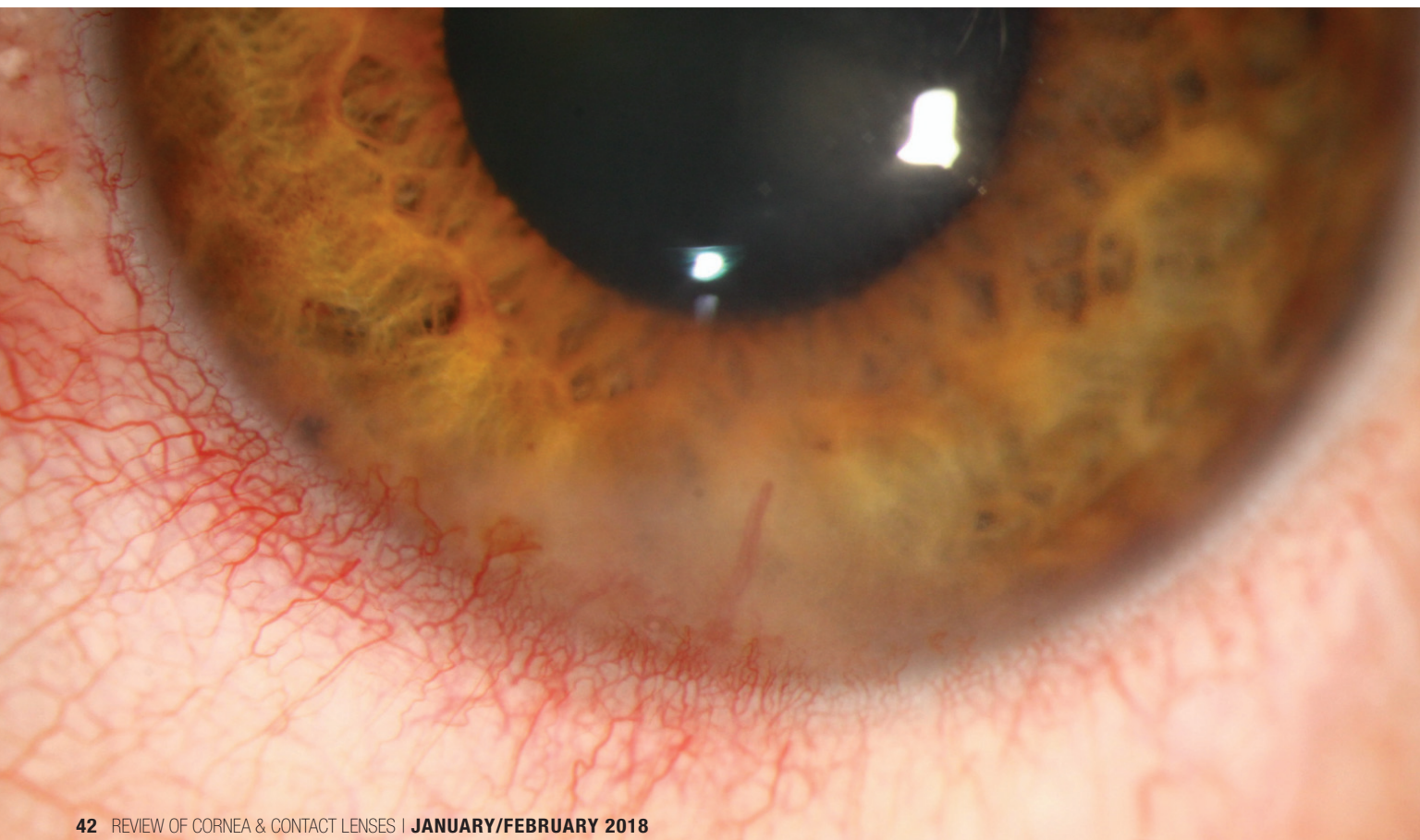

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