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Dialogues in Dry Eye

PERSPECTIVES AND INSIGHTS IN THE MANAGEMENT OF DRY EYE DISEASE

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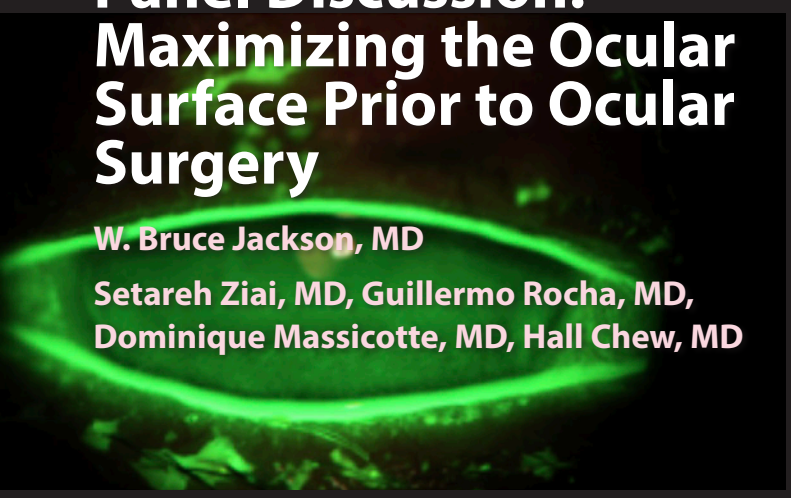

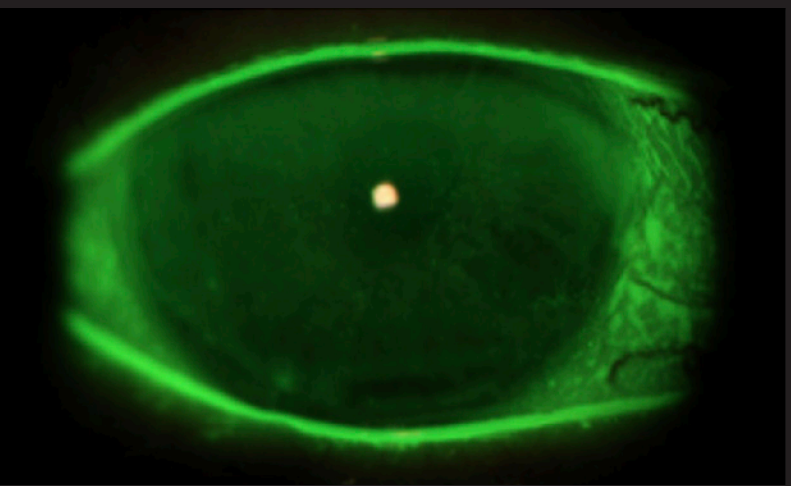

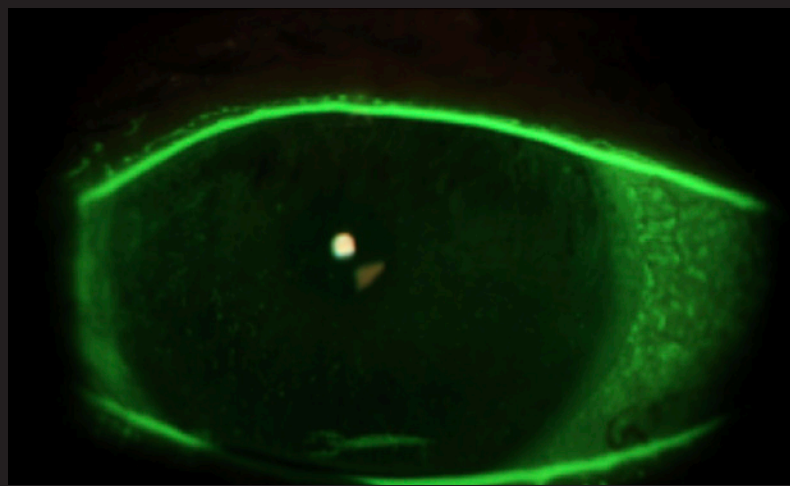

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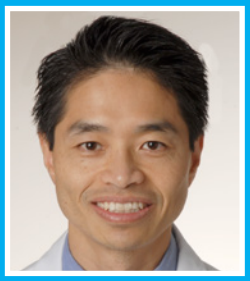

Hall Chew, MD

Dry eye disease is common as people age, and it's often asymptomatic. Ensuring the best outcomes, safety and patient satisfaction for cataract and other ocular surgeries requires careful examination and step-wise treatment of ocular surface disease.

Bruce Jackson (Moderator): When we look at The Prospective Health Assessment of Cataract Patients' Ocular Surface (PHACO) study, it revealed that most people who underwent cataract surgery had some degree of ocular surface disease. In the study, among patients with a mean age of 71, 60% to 87% with dry eye disease were asymptomatic. However, more than 70% had a tear breakup time (TBUT) of less than five seconds and 77% had corneal staining. Improving the ocular surface is necessary to determine whether patients indeed need surgery, and which surgical option will result in the best outcome.

In your practice, how important is it to examine the ocular surface prior to surgery?

Setareh Ziai: We know that ocular surface disease is more common in women, and with aging. We also know that much of cataract surgery happens in the older population. Lastly, we know that a poor ocular surface can affect short- and long-term outcomes of surgery. Knowing those facts makes it undeniable that we need to properly assess the ocular surface before any type of ocular surgery.

Guillermo Rocha: With the advent of premium lenses, it is imperative to address the ocular surface. We noticed that the measurements that we took for intraocular lens implants prior to cataract surgery were not always accurate. In addition, people would say that they could read for a few minutes and then their vision "goes away". Or they would comment that they can watch TV or drive, but when they blink, their vision can become blurry. In these cases, ocular surface disease, rather than cataracts, is what's impairing a patient's vision.

Dominique Massicotte: I often ask patients to describe their eye challenges in their own words. Often, they tell me about redness in their eyes or eye fatigue. It's important to ask about their symptoms in detail because, in some cases, moving forward with cataract surgery could exacerbate their symptoms. At the slit lamp, I like to quickly measure the tear meniscus and breakup time and then look for rosacea and meibomian gland dysfunction.

How do you treat the ocular surface prior to surgery?

Hall Chew: I encourage warm compresses and preservative-free artificial tears. If there is ocular surface inflammation, I may suggest low-dose steroids, while making sure that patients don't have any issues with infection or pressure spikes. Then, I'll have patients come back after 2-4 weeks to recalculate. Sometimes I do serial calculations to see if I can find consistency. It can be important to make patients aware of the variability, and the challenges that this poses for cataract surgery.

G.R.: We send letters to patients outlining specific lid hygiene routine, even before patients come into the office. We suggest warm compresses every day, tea tree oil cleansing, and artificial tears as needed. Many of the patients come in having already done this before they see us for an assessment. We tell patients to continue performing this routine until the time of surgery and then to start again one week post-surgery.

S.Z.: Some patients only need a little bit of what I like to call "TLC": **T**eaching them about increased humidity and less screen time, **L**ubrication, and **C**ompresses. I also recommend Omega-3 supplements.

B.J.: What about the patient that has mild lid disease, rapid tear breakup and significant corneal staining. Would you delay surgery to improve the surface

D.M.: I would treat the patient with artificial tears, ideally without a preservative. I really like gel at night. I also ask patients about how they heat their homes – wood-burning heat is especially drying – and I recommend a humidifier accordingly. If the ocular surface has improved three to four months later, I repeat the biometry. I make sure that patients continue their efforts until the surgery, explaining that the surgery will be better tolerated by them and easier for me.

H.C.: Patients don't like to delay surgery, so communication is very important. It's important to set the expectation that dry eye disease may be more symptomatic as they heal after cataract surgery, and as they taper off steroids. This helps to reinforce the importance of taking the time for good eye hygiene.

B.J.: The literature suggests that treating patients with a steroid, cyclosporine, or both, can improve the post-operative outcome, if the patient has keratitis associated with dry eye. This is something I do in my practice. Do you do this as well, with more severe dry eye patients?

S.Z.: As we get into more advanced dry eye, I bring cyclosporine, oral tetracycline, and punctal occlusion into my therapeutic armamentarium, depending on the severity of the case and the underlying cause. I also use a short course of a steroid drops for about one month before measurements and surgery. This is not ideal for long-term treatment, but it reduces some of the inflammation in order to improve our measurements and maximize our surgical outcomes.

H.C.: It's important to use steroids, when necessary, but also to explain the importance of tapering off the steroids, because chronic use can lead to glaucoma.

G.R.: If we see a significant amount of keratitis, I will use cyclosporine ahead of surgery.

B.J.: Is there anything you do differently in the operating room for patients with dry eye disease?

G.R.: We use a wick for dilating patients, so we're not always adding drops, which makes patients more comfortable.

D.M.: After the surgery, I like to put a pressure patch on those patients with severe dry eye disease and have them sleep with it the first night. This seems to lower patients' pain, because they don't open their eyes, and they don't have their eyelid rubbing on the surface that has ultimately dried during the surgery.

H.C.: I also patch the eye for patients after surgery. I usually see patients a few hours later, as my patients often tend to be discharged on the same day. When I check their eyes, I don't usually put another drop of topical anesthetic in, because that can further dry the eye. In addition, when preparing for surgery, I only put the anesthetic in the surgical eye. If you anesthetize both eyes, the blink rate will be reduced in both eyes.

B.J. Let's discuss a case. A 73-year-old male was referred for possible cataract surgery. His only complaint was decreasing vision over the past year. The initial examination revealed ocular rosacea with meibomian gland disease, 20/30 and 20/40 best corrected vision, a rapid tear breakup and central epithelial basement membrane dystrophy (EMBD) lines as well as inferior superficial punctate keratitis in both eyes. How do you manage this patient?

S.Z. I would treat the ocular surface with the TLC method I mentioned earlier and oral doxycycline or minocycline. I would also treat the EBMD with phototherapeutic keratectomy. I would expect the vision to improve significantly after these treatments, and the patient may not end up needing cataract surgery at this point. We really can't tell until we clean things up because the surface is so poor and affecting the vision in ways we cannot measure.

D.M.: Again, I would start by asking the patient to describe his symptoms. He likely thinks his red eye and burning are from his cataract, and that the surgery will fix the problem. I would explain that the ocular surface problems are separate from the cataract issue, and that he has to put effort into treating the ocular surface. I would encourage eyelid hygiene and artificial tears, and then I would start doxycycline on the second visit. If the tear film and surface hasn't improved by the third visit, I would address the EBMD with a superficial keratectomy or a PTK.

H.C. After optimizing the ocular surface, the patient may be happy with their vision and comfort level. It makes the risk-benefit decision regarding surgery more straightforward for the patient.

G.R.: This is one of the most common complex cases I see. I divide my treatment approach for these patients into two steps. First, I focus on fully treating the meibomian gland dysfunction with lid hygiene, doxycycline, fusidic acid, and lubricating drops. I bring them back three months later, and do a superficial keratectomy. I use anesthetic,

betadine, and then a lid speculum, and use a couple of dry cotton tip applicators to peel off the EBMD. I then do the biometry after another month. It's very rare that I do a phototherapeutic keratectomy on patients with EBMD.

B.J.: I also always treat EBMD before considering cataract surgery. I have seen two to three lines of improvement come just from superficial keratectomy or PTK. However, I would suggest waiting longer, as I've seen the refraction change up to three months post-operatively.

B.J.: What about patients with Salzmann's nodular dystrophy? Do you proceed with cataract surgery, or do you first remove these and let the cornea heal?

S.Z.: Topography is always helpful in knowing how much a Salzmann's nodule is affecting the vision and more importantly, the visual axis. I treat most cases of primary Salzmann's nodules prior to cataract surgery. Recurrent nodules can be trickier to treat, and are sometimes left in place, assuming they are small and relatively stable.

G.R.: We first treat the ocular surface. Then, when they come back, we peel off the nodules at the slit lamp. I take Colibri forceps and move the epithelium around, find the edge, and they simply just peel off. You don't even have to do a complete keratectomy. After a few weeks, we remeasure them.

H.C.: I usually do the removal in the treatment room, but if the treatment room is being used, we will do the removal at the slit lamp.

B.J.: What about pterygium prior to cataract surgery?

S.Z.: I would excise most pterygia prior to cataract surgery. The exception would be a very small and peripheral pterygium in an elderly patient. If the lesion is not affecting the visual axis or the corneal curvature, and has looked the same for the past 40 years, it is unlikely to become an issue anytime in the future.

H.C.: Unfortunately, you can see surgically induced necrotizing scleritis (SINS) post pterygium excision, and we recently saw a patient with a perforation as a result of surgery. So, you have to be careful with pterygium removal. But if it's affecting the vision, with no signs of corneal scleral thinning and/or rheumatological disease, it's reasonable to proceed with removing it.

G.R.: If there is significant astigmatism, especially more than 1.25 or 1.5 diopters, I would remove it.

B.J.: Do you manage patients differently if they have other corneal lesions, scars, or dystrophies, and may also have cataracts?

S.Z.: You want to ensure that keratoconus and pellucid marginal degeneration are as stable as possible prior to surgery. I would not treat other corneal conditions, such as difficult-to-treat dystrophies, small scars and early Fuchs' dystrophy. In all cases where a corneal pathology is being left untreated prior to cataract surgery, it is of utmost importance to manage the patient's expectations prior to surgery. They should know that the outcome is not guaranteed, that they may need glasses post-operatively and that their corneal condition (and thus their vision) could change over time.

H.C.: I try to avoid penetrating keratoplasties, given the risks involved with them, compared to the endothelial and lamellar transplants we can now perform. One tip I've incorporated into my practice is to use the medium setting of your light filter, make the beam very broad and look straight on. That will mimic the operating room view. If you think you can safely do the cataract surgery with that view, then you should go ahead.

B.J. This has been a very helpful discussion, highlighting the importance of thoroughly examining (not just looking at the tear meniscus), and treating the ocular surface prior to surgery. Do you have any final takeaway points?

D.M.: I would say that artificial tears are your best friend, pre-operatively and post-operatively. I always prescribe artificial tears the second month after surgery. This keeps the patient comfortable and precludes the need for many phone calls to our clinic.

H.C.: I would like to underscore the importance of avoiding the use of topical nonsteroidal anti-inflammatory drugs (NSAIDs), in patients with significant dry eyes and possible rheumatological disease which may lead to catastrophic events (i.e., corneal perforations, thinning, and scarring). Always consider that patients who have significant ocular surface disease and keratitis sicca, may have underlying rheumatologic issues (i.e., rheumatoid arthritis, Sjogren's syndrome) which can lead to permanent vision loss when topical NSAIDs are used.

G.R. In 2023, we have very good lenses and biometers for cataract surgery. The drawback is that if we don't get good data, the results will be poor. So it's necessary to optimize the ocular surface. Keratometry readings are one of the two most important variables in calculating lens powers.

ABOUT THE PANELISTS

W. Bruce Jackson, MD (Moderator)
Dr. Jackson is an ophthalmologist who specializes in cornea and external diseases, and refractive surgery. In 1986, he became Ophthalmologist-in-Chief at the Royal Victoria Hospital and in 1987, Chairman of the Department of Ophthalmology at McGill, Program Director, and Research Director, a position he held until he moved to the University of Ottawa in 1991 where he became Chairman of the Department of Ophthalmology and Director General at the University of Ottawa Eye Institute, The Ottawa Hospital until the end of his mandate, in June 2008. He is the recipient of the Canadian Ophthalmological Society and the Eye Physicians and Surgeons of Ontario's Lifetime Achievement Awards.

Setareh Ziai, MD
Dr. Ziai is an Assistant Professor of Ophthalmology at the University of Ottawa Eye Institute. She completed her residency training in ophthalmology at the University of Ottawa Eye Institute, followed by two years of fellowship training in cornea, external disease, anterior segment and refractive surgery. Her practice encompasses tertiary care clinical and surgical ophthalmology, with a focus on ocular surface disease, corneal transplantation, ocular tumour resection, anterior segment reconstruction and complex cataract surgery. She is heavily involved in clinical research, as well as resident and fellow surgical and clinical training. She is the Director of the Cornea, Anterior Segment & Refractive Surgery Fellowship Program, as well as the Director of the Ophthalmic Medical Technology training program at the University of Ottawa Eye Institute. She is also a founding member of Canadian Women in Medicine and a member of the Canadian Ophthalmological Society Board of Directors.

Guillermo Rocha, MD
Guillermo Rocha, MD, FRCSC, FACS is Medical Director of the Ocular Microsurgery & Laser Centre in Brandon, MB. He trained in Ophthalmology at McGill University in Montreal and has completed subspecialty training in Ocular Immunology and Inflammation (McGill University), and Cornea and External Diseases (University of South Florida, Tampa). He completed the Physician CEO Executive Program at the Kellogg School of Management, Northwestern University in Chicago, IL in 2016. He is Professor of Ophthalmology at the University of Manitoba, President of the COS Foundation, Past President of the Canadian Ophthalmological Society (2016-2018), past President of the Canadian Cornea, External Diseases and Refractive Surgery Society, and former Head of the Department of Surgery at the Brandon Regional Health Centre (2004-2009). In the Canadian Ophthalmological Society, he is a past Board Member and past Chair of the Council on Continuing Professional Development.

Dominique B. Massicotte, MD
Dr. Dominique B. Massicotte is a comprehensive ophthalmologist and Department Head at CIUSSS Capitale-Nationale, Quebec. She is currently an Assistant Professor at Laval University, in charge of the Ethics Course in Ophthalmology and a Wetlab instructor focused on challenging cataract surgeries. She was invited to speak about her experience on starting a new department at the first Next Gen meeting in San Diego. Passionate for continuous refinement in cataract surgery, she was part of the Faculty during the Canadian Ophthalmology Society Co-Developed Symposium, sharing pearls on the management of challenging surgical cases. Finally, while as a resident she helped create the annual All About IOLs symposium, she is now a Faculty member, dedicated to empowering the residents to better understand intraocular lens choices.

Hall Chew, MD
Dr. Hall Chew graduated from Medicine at Dalhousie University and completed his Ophthalmology Residency at the University of Toronto. He then completed a Cornea, External Disease Fellowship at the Wills Eye Hospital in Philadelphia, PA. He is a Professor in the Department of Ophthalmology & Vision Sciences, at the University of Toronto.

William Ngo, OD, PhD, FAAO

Dr. William Ngo is an Assistant Professor at the University of Waterloo School of Optometry & Vision Science. He has over 10 years of experience conducting clinical and basic research in ocular surface disease. His research interests include understanding age-related changes to the ocular surface and discovering new targets and drugs against inflammation and disease. Outside of academia, he provides specialty dry eye care to patients.

Eyelid Hygiene for the Management of Blepharitis

Introduction

Blepharitis is one of the most common conditions encountered in clinical practice occurring in up to 47% of adults in the United States).[1] Blepharitis is characterized by inflammation of the eyelids, presenting as red, edematous eyelids and margins accompanied by flaky and waxy debris, and cuffs on the eyelashes. Some patients may be asymptomatic, however, others may complain about ocular surface irritation and dryness. Many patients do not realize they have blepharitis, therefore the diagnosis of the condition is often overlooked during appointments with practitioners. In anterior blepharitis, the most common organisms present are bacteria (i.e., *Staphylococcus spp*) and mites (i.e., *Demodex spp*), causing staphylococcal and demodex blepharitis. Both types of blepharitis cause significant ocular surface irritation, although they originate from vastly different etiologies. Therefore, being able to differentiate between the two is key to their successful management.

Staphylococcus aureus is a gram positive, coagulase positive bacteria and is the causative agent for a large number of ocular inflammatory conditions, such as marginal keratitis[2] and phlyctenulosis,[3] including blepharitis. Fortunately, its ability to colonize skin is limited by other commensal coagulase negative staphylococcal (CoNS) bacteria (e.g., *S. epidermidis*). This is achieved directly by competition or indirectly by CoNS "educating" and priming the innate defences of the skin.[4] CoNS may also augment the activity of *Staphylococcus aureus*[5] and could contribute to corneal inflammatory conditions, as well.[6] While the mechanisms of the host-bacteria interaction underlying blepharitis are not well understood, it is thought that altered skin microbial composition and a high amount of bioburden play contributory roles.

Demodex folliculorum and *Demodex brevis* are culprit organisms in demodex blepharitis. Like staphylococcal bacteria, *Demodex spp* are also commensal organisms (mites).[7] They live within pilosebaceous units and have a 14-day lifecycle.[8] The extent of demodex colonization of the skin increases with age.[9] Demodex infestation is associated with other inflammatory skin conditions such as rosacea, seborrheic dermatitis and acne vulgaris.[10]

The difference in clinical manifestation between staphylococcal and demodex blepharitis may be determined by examining the eyelashes. Staphylococcal blepharitis is associated with small, crusty flakes littered across the eyelashes, whereas demodex blepharitis is associated with greasy conical or cylindrical cuffs that form at the base of the eyelashes. In moderate cases, using tweezers to strip away the cuffs can reveal the tails of demodex mites (**Figure 1**). Further, gently rotating and epilating the lashes, and viewing them under conventional light microscopy can reveal demodex mites (**Figure 2**).

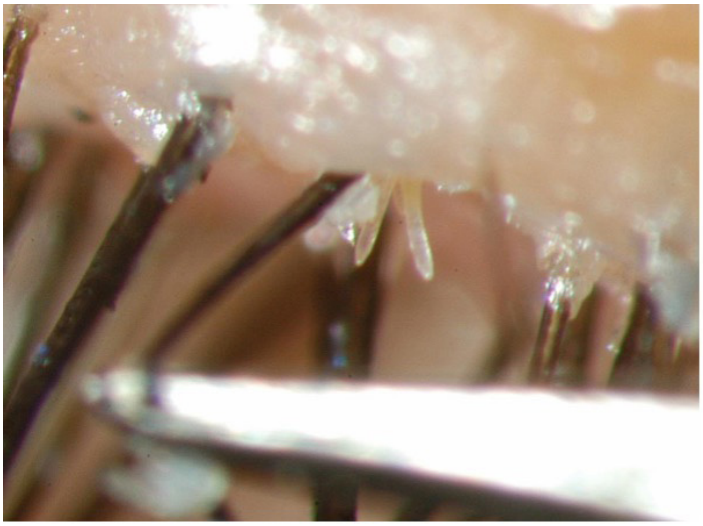

Figure 1. A pair of demodex tails can be seen when the cylindrical cuffs are stripped away and when the eyelash is pulled to the side.

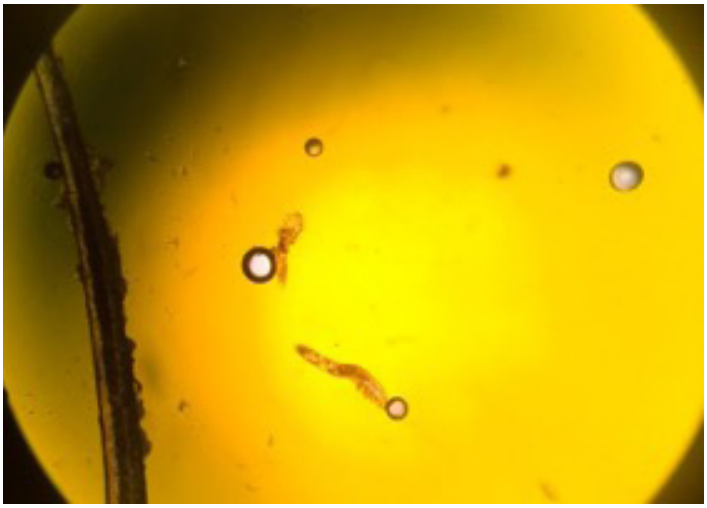

Figure 2. Two demodex mites loosened from an epilated eyelash, observed under a light microscope.

Certain types of bacteria are associated with increased demodex infestation, specifically *Propionibacterium spp*.[11] Typically, staphylococcal and demodex blepharitis manifest together. A second way to differentiate between the two is that patients with demodex blepharitis do not improve with conventional eyelid hygiene. While blepharitis is commonly associated with the eyelashes, it is important to note that blepharitis often involves the posterior eyelid margins as well, resulting in bacterial breakdown of meibomian gland lipids (saponification) and meibomitis (posterior blepharitis).

Treatment

The cornerstone of blepharitis management is eyelid hygiene, which can be carried out using a variety of commercially available products. There are countless products available and they are available in several different forms. One common form is cotton pads pre-soaked with mild detergents, foaming cleansers, gels, and mechanical brushes and applicators. The product is directly applied to the base of the eyelashes and eyelid margins, using physical agitation to loosen bacteria, debris and dead skin cells. The detergents may be synthetic or naturally derived (e.g., manuka honey or okra extract). Despite the large number of products commercially available, a recent systematic review found that while eyelid hygiene products demonstrate some efficacy, there is insufficient evidence to support greater efficacy in one product vs another.[12]

Eyelid hygiene products for treating demodex blepharitis typically contain tea tree oil, with concentrations as high as 50%. There is no consensus for the use of a specific concentration, and a recent systematic review suggested that lower concentrations may be preferable as they result in less eye irritation.[13] At low concentrations, some patients may find the treatment tolerable, and upon application may describe the sensation as "refreshing," with a "pleasant, cooling sensation". At higher tea tree oil concentrations, their use becomes increasingly uncomfortable due to burning and intense stinging.[14] A previous study demonstrated that the primary ingredient in tea tree oil for the eradication of demodex is 4-terpineol.[15] A commercial product containing 4-terpineol is available.

Hypochlorous acid (HOCl) was initially developed to clean and prevent microbial colonization during wound care,[16]; it has since been adapted for the management of blepharitis. The bactericidal mechanisms of HOCl include disruption of the bacterial cell wall and disruption of protein and DNA synthesis.[17] In a recent study, 0.01% HOCl was reported to reduce skin bacterial load without altering its diversity.[18] Currently, it is unclear whether or not HOCl eradicates *Demodex spp*. One in vitro study demonstrated that the demodex eradication time for HOCl was minimally different from that of mineral oil (the control).[19] However, a separate in vivo study reported a reduction in *Demodex spp* numbers following treatment with HOCl.[20] Additional robust research in this area would be valuable. Recently, okra extract has been used and was demonstrated as effective as tea tree oil. Additionally, okra is much more easily tolerated by patients than tea tree oil.[21]

Baby shampoo is not recommended for eyelid hygiene. While commercially available baby shampoos may relieve the signs and symptoms of blepharitis, they may contain ingredients (e.g., cocamidopropyl betaine)[22] that can trigger allergic dermatitis. One study found that while baby shampoo was successful in improving patient

comfort, it also worsened meibomian gland obstruction and mucin (MUC5AC) expression.[23] This suggests that baby shampoo may offer short-term relief, but with the caveat that it damages ocular surface health in the long term.

In promoting ocular surface health, eyelid hygiene offers benefits to patients who are contact lens wearers or are undergoing refractive surgery or intraocular lens extraction. Increased bacterial burden on the eyelids have been associated with an increased risk for the development of sterile infiltrates and other inflammatory corneal conditions.[6] These conditions compromise the contact lens wearing experience, leading to reduced lens wear comfort and wearing time for patients who are highly dependent on contact lens wear. While contact lens discomfort is highly complex and results from multiple factors, it is possible that managing blepharitis may enable those who have discontinued lens wear to resume contact lens wear. One study demonstrated that treating blepharitis using in-office microblepharoexfoliation resulted in significant improvements to tear film and contact lens comfort in symptomatic contact lens wearers.[24] A healthy ocular surface and tear film are essential in optimizing surgical outcomes and reducing the risk of complications. One study found that eyelid hygiene improves postoperative symptoms and prevents exacerbation of blepharitis and meibomian gland dysfunction in cataract surgery.[25] Reducing the microbial load through the practice of eyelid hygiene is an important complement to antibiotics in reducing the risk of postoperative endophthalmitis.[26]

Clinical Pearls

In this author's clinical experience, the majority of patients with blepharitis have never heard of or performed eyelid hygiene. They find in-office demonstration of eyelid hygiene techniques extremely helpful in promoting a better understanding of the nuances in cleaning techniques. These include appropriate pressure, duration and the sensation that accompanies scrubbing the eyelid. Therefore, it is recommended that clinicians have sample products ready for the purpose of demonstration. This is especially helpful when educating patients about tea tree oil-based products, as some patients are quite surprised at the degree of irritation they can cause. In-office demonstrations are an example of activities that, while time-consuming, are effective in fostering a strong doctor-patient relationship.

A second clinical pearl is the benefit of using slit lamp videos and photography for clinicians to share with patients what their progress looks like in visual form. Photography is a visually impactful tool and serves two purposes, at a minimum. The first is to aid in educating and counselling the patient on blepharitis, helping them understand the factors causing the redness and discomfort around their eyelids. Having patients see the demodex mites for themselves is often a powerful motivator. The second purpose is to enable patients to view their progress first-hand and to appreciate the benefits of adhering to therapy. Both of these elements help to encourage patient compliance to treatment and signify another dimension in enhancing both the quality of care the patient receives and the patient-doctor relationship.

Conclusion

With the myriad of eyelid hygiene products at their disposal, patients may easily become overwhelmed or confused about which of these to use. Compounding the situation is the fact that there is very little data or evidence available with which to gauge the relative performance of each product. Therefore, managing patient expectations and their lifestyle with regard to blepharitis can result in its effective treatment; it can feel more like a subjective art than a science. In light of this, it is valuable for clinicians to communicate to their patients why a specific treatment has been chosen for them. Over time, as patients become accustomed to their therapy, it is possible that they may adopt negative lid hygiene habits leading to ineffective cleaning. Therefore, it is recommended that clinicians occasionally follow-up with patients regarding their eyelid hygiene regimen.

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Diana Nguyen, OD

Dr. Diana Nguyen received her Honours Bachelor's of Science in Biochemistry at McMaster University and then went to complete her Doctor of Optometry at the University of Waterloo. She practices full scope optometry with a keen interest in dry eye, specialty contact lenses and myopia control. Dr. Nguyen is the Public Education Officer at MyDryEye.ca where she writes educational dry eye blogs for patients. She also plans the Dry Eye Summit year round, which is a well-established dry eye conference with leaders in the optometry field. Dr. Nguyen enjoys integrating the latest in dry eye technology to best serve her patients. She serves as a consultant for various dry eye advisory boards such as Sun Pharma, Labtician-Thea and Novartis.

Amniotic Membrane Use in Dry Eye

Introduction

Dry eye disease (DED) affects approximately 30% of patients and is a common complaint in optometry clinics. The most common type of dry eye is meibomian gland dysfunction (MGD) which accounts for up to 80% of dry eye patients. In addition, inflammation plays a significant role in the pathogenesis of dry eye due to the presence of pro-inflammatory cytokines and chemokines.[1] Patients who are symptomatic often experience visual fluctuations and severe ocular irritation.

Fortunately, there are various treatment modalities that can address MGD and inflammation. Heat pulsation therapies such as Lipiflow,® iLux® and Radio frequency (RF) unclog oils, while low-level light therapy (LLLT) and intense pulsed light (IPL) help reduce ocular inflammation.

For patients with moderate to advanced keratitis and corneal neuropathy, dry eye management becomes increasingly difficult as the cornea is more severely compromised. The dry eye clinician should consider adding amniotic membrane (AM) as part of the multimodal approach in the treatment of advanced cases of DED. AM has been shown to have a potent anti-inflammatory effect, as well as the ability to restore corneal nerve density.[2,3] The biological properties of AM will be reviewed and an overview of its use in DED will be provided.

Explanation of Amniotic Membrane

AM is derived from the innermost lining of the placenta and is approximately 0.02 to 0.5 mm in thickness. It is created by the same cellular origin of the fetus and contains three major layers: the monolayer epithelium, the basement membrane and an avascular stroma. Prior to manufacturing, the tissue must be tested to eliminate pathogens such as human immunodeficiency virus (HIV), hepatitis B, hepatitis C, Human 1-lymphotropic virus (HTLV) and syphilis. AM is packaged and prepared in a sterile environment to minimize contamination. Donor tissues are provided by women with planned Cesarean-sections. Once it has been properly preserved and has passed strict safety protocols, the AM is ready for in-clinic use.[4]

Biological Properties of Amniotic Membrane

The primary objective of the AM is to promote corneal epithelialization, minimize pain and reduce inflammation on the ocular surface. Type VII collagen and laminin in the AM basement membrane promote epithelialization.[5] Additionally, heavy-chain (HC)-hyaluronan (HA)/pentraxin 3 (PTX3) proteoglycan complex is one of the main biochemical tissues in AM that assists in corneal healing. HC-HA/PTX3 facilitates rapid clearance of neutrophils to resolve chronic inflammation, expresses significant amounts of anti-inflammatory IL-10, and suppresses T-cell proliferation and activation.[6] Evidence has also demonstrated its anti-scarring capabilities by inhibiting myofibroblast differentiation and downregulating transforming growth factor-beta (TGF-β) signaling.[7,8]

Additionally, John et al. reported a significant increase in subbasal corneal nerve density and corneal sensitivity following AM treatment. Corneal nerve regeneration restores corneal punctate staining and improves tear film stability.[9] As well, AM has overall anti-inflammatory and

anti-scarring properties, and the ability to regenerate corneal nerves.[10]

Amniotic Membrane Indications in Dry Eye

The most well-known indication for AM is for disorders of the cornea. It plays a significant role in treating various anterior segment disorders such as bullous or band keratopathy, acute chemical burns, corneal erosions, Stevens-Johnson syndrome, and conjunctival reconstruction in surgical glaucoma cases.[11]

The clinician should utilize it in patients with neurotrophic keratitis (NK) and chronic superficial keratitis (SPK) secondary to Sjogren's Syndrome (SS). The amniotic epithelium and stroma contain growth factors such as hepatocyte growth factor, keratinocyte growth factor and nerve growth factor, all of which has been shown to promote epithelialization and corneal healing.[12,13] The wound healing properties of AM also upregulate epithelial cell proliferation to reduce SPK (**Figure 1**).

Lastly, current management for corneal neuropathy is limited, but AM is one of the promising treatments for those suffering. Corneal nerve regeneration has been demonstrated in AM and accelerates the ocular surface of chronic dry eye patients. These patients should utilize AM in conjunction with other dry eye therapies as they most likely suffer from other subtypes of DED such as MGD and chronic inflammation.

Amniotic Membrane Treatment Protocol

When choosing an AM in the clinic, there are two available forms: cryopreserved or dehydrated tissue. Cryopreserved AM (Prokera®, BioTissue, Miami, FL) is stored frozen and must be dethawed to room temperature prior to insertion.

1. The tissue is attached to a Poly methyl methacrylate (PMMA) ring and it must be rinsed thoroughly with saline to remove preservatives (**Figure 2**)

2. After the AM has been rinsed, the clinician should thoroughly wash their hands and wear sterile gloves before application.

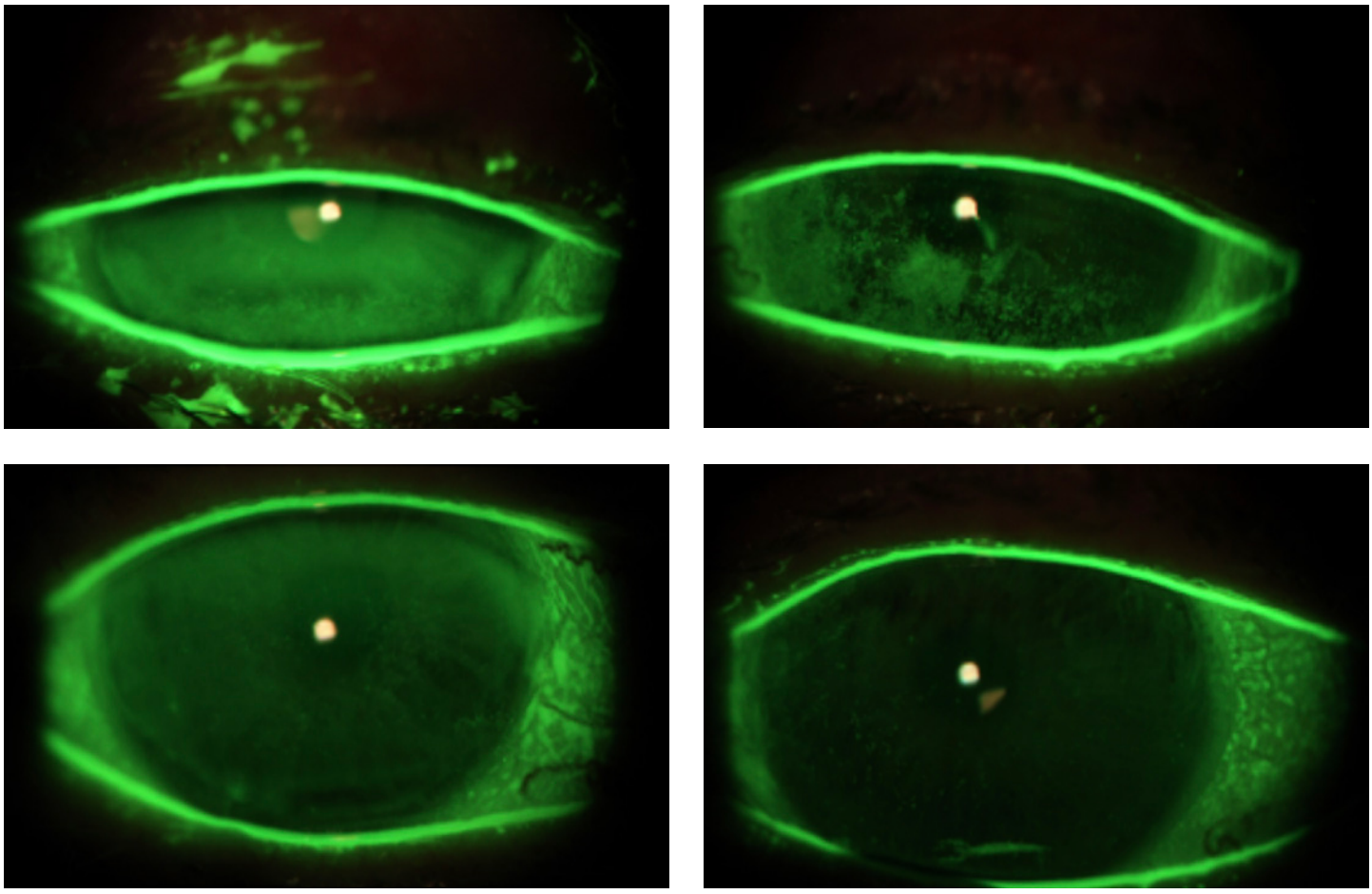

Figure 1. Chronic SPK in NK prior to AM treatment (top) and post-AM treatment with significant reduction in SPK and wider palpebral fissure due to increased ocular surface comfort (bottom); Courtesy of Diana Nguyen, OD.

3. Instill proparacine and recline the patient's chair. Insertion is more comfortable in free space as it is similar to inserting a contact lens

4. Patients may feel discomfort due to the PMMA ring, but tape tarsorrhaphy will minimize the lens movement. The clinician can use a medical grade tape to reduce the movement.

5. The AM usually dissolves within 3 to 7 days, but the patient must return to the clinic to remove the PMMA ring. Again, removal is similar to removing a contact lens. It is important to inform patients that their vision will be hazy until the AM adheres to the cornea.

Dehydrated AM (LabAmnio™, Labtician, Oakville, ON) is safely preserved by gently air-drying the allograft tissue while maintaining the AM's key properties (**Figure 3**). It can also be stored at room temperature with a shelf life of 3 years and does not need to be rinsed or thawed prior to application. Due to its dehydrated nature, insertion differs slightly from that of the cryopreserved AM.

1. The clinician will need an eye speculum, a tweezer, a Weck-Cel® cellulose spear and a bandage contact lens

2. Insertion involves instilling proparacine, reclining the patient's chair and inserting the eye speculum on the indicated eye

3. Carefully remove the dehydrated AM from its package with tweezers. The dehydrated AM may curl up as it approaches the cornea due to difference in temperatures of the room and the cornea.

4. Use a soaked Weck-Cel with saline to evenly distribute the AM on the cornea

5. Lastly, insert a bandage contact lens overtop of the AM. You may prescribe a prophylactic topical antibiotic for 7 days. In 3-7 days, the AM will dissolve and the bandage contact lenses will need to be removed. Vision will be hazy but there is usually no discomfort.

Limitations of Amniotic Membrane

Adding AM into a clinician's dry eye management armamentarium is exciting, but there are limitations with its usage. Cryopreserved AM cannot be used for patients with filtering blebs or glaucoma drainage devices. However, there are no limitations with blebs or drainage devices with dehydrated AM as there is no PMMA ring.

Additionally, patients with any active infections should be treated prior to application. Prescribe 7-10 days' worth of prophylactic oral antivirals to reduce the occurrence of HZO re-emerging for patients with a past history of herpes zoster ophthalmicus (HZO).

A patient with severe blepharospasm is not a good candidate for AM as insertion and removal will be extremely difficult. However, if the clinician believes AM would greatly improve their corneal conditions, the patient could practice inserting and removing a soft contact lens in the office with a staff member. This can help reduce anxiety so the patient can understand the essence of the AM process.

Figure 2. Cryopreserved AM with PMMA ring; Courtesy of www.Biotissue.com.

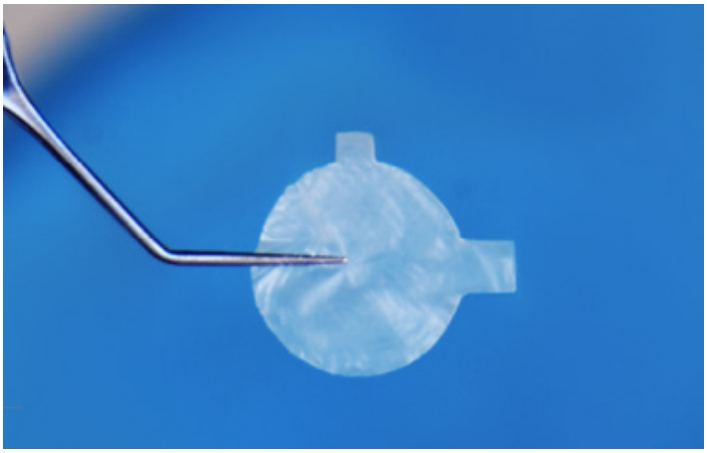

Figure 3. Dehydrated AM; Courtesy of www.labtician.com

Conclusion

Approaching DED with a multi-modal strategy will provide the best outcome for dry eye patients. One branch of the multi-modal approach is adding AM to the dry eye treatment tool box. AM acts as a self-retained biologic corneal bandage lens to suppress inflammation, promote epithelial healing and corneal nerve density growth. The treatment of severe DED with AM is especially promising for the clinician and the patient as current research illustrates its unique and positive impact on the cornea.

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