Issue 4

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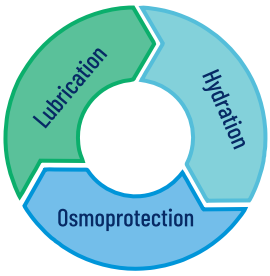

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1. Mike Christensen, OD, PhD, and Tressa Larson, OD, Artificial Tears: Looking Beneath the Surface, Review of Cornea and Contact Lenses, February 2016

*Source is Natural Producer of HA (streptococcus equi sub. zoopidemicus)

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Dry Eye

Springer Healthcare Education

October 2019

Springer Healthcare

This edition is published by Springer Nature India Private Limited.
Registered Office: 7th Floor, Vijaya Building, 17, Barakhamba Road, New Delhi 110 001, India.
T: +91 (0) 11 4575 5888
www.springerhealthcare.com

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Aqueous-deficient Dry Eye Disease: Evaluation and Management

Benjamin Botsford, Farhan I. Merali, Samuel C. Yiu

Case 1

BJ is a 52-year-old female who complains of tearing, burning, and a gritty feeling in both eyes for the last year but with progressive worsening of severity. The patient notes that it has become increasingly difficult for her to read books, as she develops increased burning. She also notices that her eyes feel worse on windy days. She has a past medical history of hypertension and takes hydrochlorothiazide. She has no prior ocular history besides being myopic and sees an optometrist for examination and refraction every 2 years. She has not yet tried anything to relieve her current symptoms (Table 1).

What Additional Questions do you Want to ask this Patient to Further Understand the Possible Etiology of her Complaints?

The patient's initial complaints are very suggestive of dry eye disease. The symptoms of dry eye disease vary among patients, but may include tearing, burning, the sensation of dryness, sensitivity to light, transiently blurred vision, and foreign body or gritty sensations. Exacerbation with activities like reading or watching TV that cause reduction in blink frequency or by environmental factors such as heating, air conditioning, and wind can be suggestive of dry eye disease. Symptoms are often worse toward the end of the day, with the exception being nocturnal lagophthalmos in which case morning is usually worse. The initial evaluation for a patient with these symptoms

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Table 1: The DEWS dry eye diagnosis and management grid[a].

Dry eye severity level	1	2	3	4
Discomfort, severity, and frequency	Mild/episodic/ environmental stress	Moderate/episodic or chronic/environmental stress or no stress	Severe/frequent or constant without stress	Severe and disabling, constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic, and/or constant limiting activity	Constant and/or possibly disabling
Lid/meibomian glands	MGD variably present		Frequent	Trichiasis, keratinization, symblepharon
TFBUT (s)	Variable	≤10	≤5	Immediate
Corneal staining (NEI Scale 0–15)	None to mild	Variable	Central	Severe punctate erosions
Conjunctival staining (NEI Scale 0–18)	None to mild	Variable	Moderate to marked	Marked
Schirmer's test (no anesthesia) (mm/5 min)	Variable	≤10	≤5	≤2
Recommended management	1. Patient education	Add:	Add:	Add:
	2. Diet modification	1. Anti-inflammatories	1. Autologous serum	1. Systemic anti-inflammatory agents
	3. Lid therapy		2. Bandage or large-diameter rigid contact lenses	
	4. Artificial tear/gel supplements	2. Tetracycline		
		3. Punctal plugs		
	5. Environmental control	4. Moisture chamber spectacles	3. Permanent punctal occlusion	2. Surgical intervention

[a]Modified with permission from 2007 DEWS report [38]

may be difficult as symptoms may be heterogeneous or vague. A full and comprehensive history should be taken, including identification of potential exacerbating factors, such as medications or environments, and patient behaviors, as discussed below.

Questions about the patient's work environment should be conducted, as well as inquiring about activities that require visual concentration, such as reading or working on a computer. Computer use is associated with a decrease blink frequency through suppression of blinking, causing prolonged exposure of the ocular surface and disruption of the tear film [1]. Identifying the number of hours the patient may read or look at a computer monitor is useful for recognizing exposure as a risk factor and for elucidating potential behavioral modifications that may benefit the patient. Additional environmental factors such as direct exposure to ventilation can worsen symptoms, and desiccating environments involving heat or air conditioning may precipitate or worsen dry eye disease.

Other risk factors may include female gender and old age. Postmenopausal patients presenting with dry eye symptoms should be queried about possible hormonal replacement therapy, as

replacement with either estrogen or estrogen and progestin has been shown to increase the risk for developing dry eye [2].

Any medications that the patient takes should be carefully evaluated. Ocular medications, especially glaucoma medications containing the preservative benzalkonium chloride [3, 4] have been shown to precipitate dry eye disease by causing tear film instability, loss of goblet cells, conjunctival squamous apoptosis, and disruption of the corneal epithelial barrier [5]. Systemic medications such as antihistamines, systemic retinoids, antidepressants or antianxiety medications with anticholinergic side effects, as well as diuretics may cause or contribute to a patient's symptoms. Asking a patient if they have recently started any new medications and determining temporal relation in regard to their symptoms may be useful in identifying problem medications that should be discontinued or substituted.

While allergic conjunctivitis is not typically a component of dry eye disease, symptoms of the two entities may overlap. It is therefore important to inquire about environmental allergens and a history of seasonal allergies. It is also useful to elicit the presence of symptoms of allergic conjunctivitis, such as itching and eye rubbing. Avoidance of allergens or other irritants may be a useful intervention for relieving symptoms that may be attributable to those causes.

Contact lens wear should be assessed, as use can be a significant contributor to for dry eye disease. The patient should also be asked about any prior history of refractive surgery. Postoperative corneal hypoesthesia caused by the resection of corneal nerves during surgery can lead to dry eye through a decrease in reflex tear secretion. Usually, corneal nerves will regenerate postoperatively but may leave the patient with dry eye symptoms for multiple months before healing occurs [6].

For any patient presenting with symptoms of dry eye disease, it is important to rule out systemic causes as the underlying etiology (Fig. 1). Any history of chemotherapy or radiation should be elicited as these treatment modalities can damage the lacrimal and meibomian glands and cause hypofunction, leading to aqueous deficient dry eye disease (AD-DED) as well as evaporative dry eye. A thorough review of systems should be conducted with the following disease processes in mind, as they can cause ocular surface dryness: diabetes, rheumatoid arthritis, hepatitis C, HIV, sarcoidosis, thyroid disease, lupus, Sjögren syndrome (SS), graft-versus-host disease, and cicatricial pemphigoid. It is prudent to question about fatigue, joint problems, dry mouth, vaginal dryness, skin lesions or rashes, shortness of breath, hearing loss, urinary difficulties, headaches, fever, peripheral edema, and peripheral neuropathy to work up these systemic conditions, as treatment will need to address the underlying condition. History of snoring and daytime sleepiness should likewise raise the suspicion for sleep apnea (often in patient with lax eyelids). The ophthalmologist may very well be the first provider to diagnose a systemic condition associated with dry eye. SS is a particularly important consideration in the initial assessment of a patient as prevalence of primary SS may be as high as 10–11% in patients presenting with clinically significant AD-DED [7]. Questions about family history of autoimmune diseases can also provide further clues. Positive review of systems concerning for systemic illness necessitates further investigation and/or referral.

The patient works as a secretary at an elementary school and uses her computer frequently throughout the day. Additionally, she sits close to a heating vent. She often uses

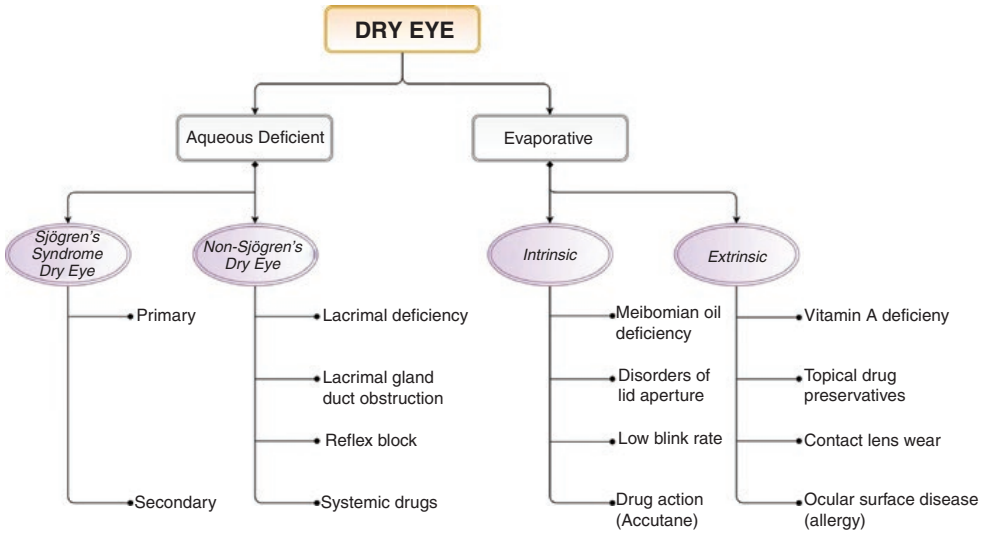

Fig. 1: Etiopathogenic classification of dry eye disease.

over-the-counter Benadryl to help her sleep. She does not wear contact lenses and denies any other medications. She denies any arthritis, rashes, dry mouth, vaginal dryness, peripheral neuropathy, or fatigue. Family history is negative for any autoimmune diseases. She smokes half a pack of cigarettes per day.

What Should you Look for on Physical Exam to Aid in Diagnosis of the Patient?

As typical of any patient, best corrected visual acuity (BCVA) should be assessed. BCVA may be diminished or may transiently fluctuate in patients with dry eye as due to tear film instability [8]. The tear film contributes to the refractive power of the cornea, and disruptions may produce higher-order aberrations that interfere with visual acuity. Dry eye patients often complain of a reduction in visual acuity with driving, reading a computer, and maintaining gaze as the ocular surface may dry out from suppression of the blink reflex. Assessment of functional visual acuity (FVA), or the measure of visual acuity during sustained eye opening without blinking, may therefore be a good tool for assessment of dry eye patients [9]. FVA has been shown to be diminished in both SS and non-SS dry eye disease [10].

An external examination of the patient should be conducted to evaluate for any evidence of rosacea, enlarged lacrimal glands, or Bell's palsy. Eyelids and lid margins should be investigated as for evidence of blepharitis, meibomian gland dysfunction, infrequent or incomplete blink, and lagophthalmos as these conditions may be addressed individually. Careful evaluation of the conjunctiva should also be conducted, and chemosis, chalasis, injection, scarring, forniceal foreshortening, subepithelial scarring, and the presence of papillae or follicles should be noted. Lid eversion should be performed. Meticulous examination may demonstrate other causes of the patient's symptoms unrelated to dry eye disease.

The tear film should be evaluated, including the size of the tear meniscus and the tear breakup time (TBUT). TBUT is conducted by instilling a small amount of fluorescein in the inferior cul-de-sac, followed by evaluating the stability of the tear film after the patient blinks. Blinking distributes the tear film across the ocular surface, and a broad beam of cobalt blue light at the slit lamp can be used to assess the time it takes from the last blink until the first dark patch appears, which represents tear film dissolution. Patients with AD-DED have significantly faster tear breakup times, with times of less than 10 s considered to be abnormal.

Ocular surface staining is another important tool used to assess dry eye severity. Staining can be used to identify abnormalities of the corneal surface and of the bulbar conjunctiva. Punctate staining of the inferior cornea and inferior bulbar conjunctiva are the most typical pattern seen in dry eye. Multiple stains can be used. Fluorescein is the most common and will stain areas of the conjunctiva and cornea where tight junctions have been disrupted, though corneal staining will be much more prominent. Peak staining occurs approximately 2 min after instillation. If conjunctivalization of the cornea has occurred, however, fluorescein staining will have limited utility.

Lissamine green and rose bengal dyes can be used to stain devitalized cells and allow for more prominent staining of the bulbar conjunctiva. These dyes may pick up more subtle changes and are useful for detecting milder forms of dry eye disease. Inferior staining may suggest MGD or exposure, while superior staining suggests superior limbic keratoconjunctivitis. Lissamine green possesses advantages over rose bengal as it is less toxic to the ocular surface [11].

On examination, visual acuity is 20/25 in both eyes with correction. Pupils are equal, round, and reactive without afferent pupillary defect bilaterally. Intraocular pressure (IOP) is 15 mmHg on the right and 16 mmHg on the left. Her lids and lashes appear normal with no evidence of meibomian gland dysfunction, lagophthalmos, or other findings. Her conjunctivas are normal. The patient's tear meniscus appears reduced, and her tear breakup time is 10 s. Corneal staining with fluorescein reveals no punctate epithelial erosions, while lissamine green reveals minimal punctate staining of the bulbar conjunctiva in the exposure zone bilaterally.

What Additional Ancillary Testing Would be Appropriate?

The Schirmer's test is the classic test for diagnosis of decreased lacrimal secretion of the aqueous portion of the tear film. The Schirmer's test is performed by placing a strip of paper in the inferior cul-de-sac and allowing the strip be wetted by produced tears over a period of 5 min. A positive Schirmer's test is <5 mm of wetting with anesthetic and <10 mm without anesthestic [12], as anesthetic will reduce reflex tear secretion. Performing the Schirmer's test with anesthetic has been shown to have more variable results than without [13]. The relatively low cutoff of the Schirmer's test produces greater specificity at the cost of decreased sensitivity. The results of the Schirmer's test may be variable between visits and should not be used as the sole criterion for diagnosis of AD-DED. However, serially abnormal results over time are highly suggestive.

Considering the importance of tear hyperosmolarity in the pathogenesis of dry eye disease, directly measuring tear osmolarity has been implemented in clinical practices since FDA

approval of the osmolarity measuring device (TearLab, San Diego, CA) in 2009. It has reported to be another test to consider as part of an overall diagnostic picture [14]. Elevated tear osmolarity is suggestive of dry eye disease, and hyperosmolar tear stress the ocular surface leading to inflammation and perpetuation of the condition. Values >312 mOsm/L were found to be 73% sensitive and 92% specific for dry eye disease in one study; [15] however, tear osmolarity values may not be correlated with symptoms [16], and some studies also suggested variability in measurements [17]. However, the variability of the measurements may actually be diagnostic of an unstable tear film and hence dry eye disease. Overall, the role of tear osmolarity in the diagnosis and monitoring of dry eyes is evolving and with further studies will likely play a role in the management of the disease.

Overall, no perfect test or examination finding exists to confirm the diagnosis of dry eye disease. Heterogeneity of patient symptoms, poor correlation of symptoms with exam findings [18] and test results, and variability of exam findings and tests between visits [19, 20] can provide substantial challenges for the ophthalmologist. The overall picture generated from the patient's symptoms, exam findings, and ancillary testing must be synthesized to provide increased sensitivity and specificity in diagnosis.

The patient's Schirmer's test without anesthesia is >20 mm. You check her tear osmolarity and find it to be 310 mOsm/L.

What Treatment Should be Initiated?

Due to the poor correlation between symptoms and signs/test findings in dry eye disease, particularly in mild dry eye disease, the patient's ancillary testing findings should not prevent any interventions. Patients with suggestive symptoms should be placed on trial treatments if other potential etiologies for their symptoms have been ruled out. Our patient should be informed that though the symptoms may improve with lifestyle changes and treatment, the condition is not typically cured but managed.

The initial approach should involve identification of environmental and behavioral risk factors and suggestion of appropriate modifications, as well as initiation of artificial tear supplementation. Scheduling a follow-up visit to assess success of these interventions is prudent, and remaining patient and optimistic is important as disease management can be challenging and punctuated by signs or symptoms that are refractory to treatment.

For aid with desiccating environments, the use of humidifiers may alleviate symptoms caused by excessive heat or air conditioning. Additional care should be taken to improve the dynamics of air movement in an office environment, and work stations may be moved out of the direct line of ducts and vents. Long hours of work on computers should be interrupted by regular breaks. Additionally, placing the monitor below eye level can decrease the interpalpebral aperture, limiting the surface area of the exposed ocular surface, thereby aiding in reduction of tear film evaporation [21].

Smoking cessation counseling should be provided as cigarette use has been found to have adverse effects to the precorneal tear film [22, 23], including the lipid layer [24]. Identifying any

offending drugs such as diuretics and anticholinergic medication as discussed above and having patients stop or consider alternatives is important. Discontinuing the Benadryl and following up with her PCP to find other sleep aids that do not have anticholinergic effects will likely be beneficial. Finally, we encourage patients to drink ample amounts of fluids.

Over-the-counter artificial tear supplementation may also be initiated. There are no significant differences between different brands and formulations of artificial tears, and patients can take whichever brand they prefer. While artificial tears without preservatives are preferred, their cost makes them prohibitive unless they become necessary. Artificial tears are generally safe in patients who use them up to four times a day. Ideally, ocular surface lubrication should be done before the patient starts to have symptoms related to ocular surface damage. Instructing the patient to use them three times a day before meals may provide a good aid to remember to use them regularly. Additionally, instructing to instill drops before reading or visual display terminal use may also help prevent exacerbations of symptoms.

You recommend behavioral modifications, asking her to take more frequent breaks from the computer, quit smoking, and move her desk away from the heating vent. She expresses desire to purchase a humidifier for her office, and you advise her to take artificial tears as needed up to four times a day to help with her symptoms. You schedule her for a 4-month follow-up visit and advise her to contact you sooner if further problems arise.

Four months later, she notes improvement with her symptoms at work. She is much more comfortable in her office and takes artificial tears before starting computer work and a couple of times after lunch, as her symptoms are worse in the afternoon. She notes that taking them before her eyes feel dry seems to provide additional benefit in prevention of her symptoms. While she has struggled to quit smoking, she has been able to cut down on the number of cigarettes she smokes a day and has discussed cessation options with her primary care doctor to assist her.

Her exam is unremarkable with no PEEs and a TBUT of 13 s. You schedule her for a yearly follow-up visit and wish her well and advise her to continue with her current regimen.

Case 2

RR is a 70-year-old male with past medical history of diabetes mellitus type 2, glaucoma, and dry eye disease here for a follow-up appointment for further management of his dry eye disease. He reports feeling a sensation of dryness and sensitivity to light and has been unable to watch television for extended periods of time due to burning and blurring of vision. For the last 6 months, he has been using over-the-counter artificial tears without any relief. He reports that he is requiring them up to six times per day. He placed a humidifier in his room and has attempted to take frequent breaks but has not noticed any difference. He also notices that he has eye irritation first thing in the morning when he wakes up. His current medications include metformin, glyburide, latanoprost, and artificial tears with preservatives. His last hemoglobin A_{1C} was 8.6.

On examination, his visual acuity is 20/40 bilaterally with spectacle correction. His IOP is 20 mmHg bilaterally. External exam and lids and lashes are normal. He has mild conjunctival injection bilaterally and no evidence of lid margin disease. TBUT is 8 s and he has 2+ PEEs on his inferior cornea on fluorescein staining. Schirmer's test performed without anesthesia is 6 mm and his tear osmolarity is 318 mOsm/L.

What are the Patient's Risk Factors for Dry Eye Disease, and How can These be Addressed?

The patient's diabetes mellitus may be contributing to his dry eye disease. Dry eye is more prevalent in diabetics, especially those with poor glycemic control [25]. Diabetes can cause corneal hypoesthesia that is correlated with decreased tear secretion [26]. Corneal sensation can be tested to identify a potential source of decreased reflex tear secretion. Better management of his diabetic care by his primary care physician is necessary and may prevent additional sequelae of the disease, and a careful retinal examination should also be conducted.

His glaucoma medications may also be a contributing factor. Benzalkonium chloride in the drops combined with the preservatives in the artificial tears may contribute to dry eye disease [3, 4]. Switching to preservative-free glaucoma drops may assist in reduction of his symptoms. Additionally, switching to preservative-free artificial tears may be necessary, as he is requiring artificial tears more than four times a day. A nighttime lubrication ointment should also be started to provide ocular surface lubrication at night, as the patient is experiencing symptoms upon awakening.

What Additional Treatments may be Initiated?

In patients with moderate dry eyes, a key question is what role inflammation is playing? While some patients may display signs of inflammation on exam, this may not always be the case. A useful test to determine the role of inflammation is to measure MMP9 levels in the tears (InflammaDry). A positive test helps to guide the therapy more toward controlling inflammation, although patients with a negative test should also be considered for anti-inflammatory therapy.

An easy first choice for targeting inflammation is Omega-3 fatty acid. A recent meta-analysis concluded that Omega-3 supplements improve the TBUT and Schirmer's test without significant change in ocular surface disease index assessment of patient symptomatology [27]. The inconsistency of the results may be in part related to the difference in the formulations and dosages used in various studies. A very recent multicenter placebo-controlled study found significant improvement in the signs and symptoms of dry eyes using a re-esterified formulation which presumably improves absorption [28]. Patients should be advised to look for fish oil formulations that provide at least 500 mg of EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) per day. As an alternative, we recommend at least three servings of fish high in Omega-3 (salmon, tuna, and halibut) per week. Flax seeds, chia seeds, and walnuts also contain Omega-3, but this is in the form of alpha-linoleic acid which must be converted to EPA/DHA in the body—a process that

is not very efficient. Therefore, these plant sources may not be as efficient and we recommend primarily fish sources.

Corticosteroids can provide immense relief of dry eye symptoms due to their immunomodulatory actions. However, side effects limit their use to short-term courses. Repetitive short-term pulsatile administration of topical corticosteroids is a promising method of harnessing their beneficial effects, while minimizing the risk of adverse events [9]. Loteprednol (or fluorometholone) is our first choice, as it provides higher potency with a lower side effect profile. A 2-week course of loteprednol or FML TID can help suppress inflammation followed by a slow taper off or down to 1–2 drops per week. If available, a preservative-free steroid (e.g., compounded methylprednisolone) may be used instead as it minimizes the detrimental effects of the preservatives. Either way, a positive clinical response to steroids confirms that inflammation is contributing to the signs/symptoms of that patients, and therefore they may be a good candidate for Restasis (and/or Xiidra) as the steroids are tapered off.

Restasis (topical cyclosporine A 0.05%) exerts immunosuppressive and anti-inflammatory actions through various pathways, but primarily by suppressing T cells. Restasis is a great option for a number of patients, though it often requires a long-term commitment and presents high costs. As such, it should be initiated with some discretion. Restasis may be initiated in patients who have persistent dry eye symptoms despite behavioral modifications, ample artificial tear supplementation, use of nighttime ointments, or dietary modifications. Additionally, these patients should display evidence of decreased tear production, as shown by elevated tear osmolarity or decreased Schirmer's test values. As noted above, one strategy may be to first try a course of topical steroids and, if the patient responds, then consider Restasis for long-term anti-inflammatory therapy. Kick-starting anti-inflammatory therapy with steroids seems prudent given that Restasis is less efficient at suppressing active inflammation.

Our experience with Restasis suggests that patients may sometimes take up to 6 months to reach its full benefit. The dose can be increased to three to four times a day to achieve further benefit, though this can precipitate worsening side effects of burning [29, 30]. Recently, another medication lifitegrast (Xiidra) has been approved as an anti-inflammatory therapy for dry eye disease. The experience at this time is limited, although the results from the clinical trials are very promising for moderate dry eye patients.

Another useful measure in this patient, or any patient on BAK-preserved glaucoma drops, is to switch to preservative-free options. We have had a number of patients who have noted improvement in their signs and symptoms from this change.

Punctal occlusion may also be a consideration in a patient whose signs and/or symptoms are not adequately controlled with anti-inflammatory therapy [31]. Prior to this step, it is best to treat acute inflammation as inflammatory mediators present in the tear film will linger longer if tear drainage is blocked, potentially exacerbating symptoms and causing further damage to the ocular surface. Initiation of Restasis and a short course of topical corticosteroids before insertion of the plug can help alleviate these concerns. It is important to inform the patient that punctal plugs will frequently dislodge but can be reinserted. Absorbable and nonabsorbable plugs made of silicone or thermal labile polymer are available. Silicone plugs provide added utility as they are removable if the patient develops epiphora or irritation. Insertion of the largest plug that fits into the duct

helps prevent plug dislodgement. As benefit from punctal occlusion has been shown to not peak until approximately 8 weeks after placement, a period of follow-up of at least this length is recommended to assess the patient's maximal response to therapy [32].

For patients with moderate disease (level 2), typically occluding only one of the puncta in each eye is considered since occluding both upper and lower will quite likely lead to epiphora. We prefer to use lower punctal silicone plugs for most patients, although collagen or other dissolvable plugs can be used for a "trial" period. Silicone plugs may be left in if the patient expresses benefit or removed if no improvement is seen. In patients who experience epiphora, perforated plugs (flow through) are an attractive option. The choice of plug remains the practitioner's preference. Permanent cauterization is reserved for patients who express benefit from punctal plugs but require frequent replacement, often due to plugs dislodging and sometimes irritating the ocular surface.

You suggest that he should begin artificial tear supplementation with preservative-free artificial tears. Since he also has symptoms upon awakening, you prescribe him a nighttime lubricant eye ointment. Additionally, you inform him that the preservatives in his latanoprost may also be contributing to his condition. You recommend he discuss with his glaucoma doctor switching to a preservative-free formulation. You also advise him that he may benefit from Omega-3 supplementation.

Lastly, you inform him that his diabetes can also contribute to his condition. You recommend he follow up with his primary care physician to help determine how he can optimize his glycemic control. You schedule him for a 3-month follow-up and advise him to come sooner if any issues arise.

Three months later, he returns. He reports mild improvement with the changes in his medications and dietary changes. He states he began taking a fish oil supplement that he found online, has been using PFATs six to seven times per day, has been using a nighttime lubricant gel, and has made further dietary modifications with slightly better glycemic control. However, he notes the symptoms are still highly bothersome and that the PFATs only seem to provide brief benefit. On examination, his TBUT is now 9 s and he has 2+ PEEs on his inferior cornea on fluorescein staining. Schirmer's testing performed without anesthesia is 5 mm and his tear osmolarity is 315 mOsm/L.

You advise the patient that he would likely benefit from Restasis. You start him a bi-daily administration and advise him that the most common side effect is a burning sensation. You tell him he may consider refrigeration of the drops and repeated use of a vial over the course of 1 day to save costs. You make note that the medication may often take a long time before he experiences benefit and that some patients may take 6 months to even a year. You avoid prescribing him a short course of steroids due to his history of glaucoma. He is scheduled for another 3-month follow-up to assess his response to the medication.

Upon follow-up, he reports improvement in his symptoms. He feels he is using his PFATs less frequently, now four to five times a day. On examination, his TBUT is 11 s and he has trace PEEs on exam on the inferior cornea. Schirmer's testing performed without anesthesia is 9

mm and his tear osmolarity is 312 mOsm/L. You advise him he is likely benefitting from the medication and schedule a 6-month follow-up appointment. In the future, you may consider punctal plugs (inferior only) if his symptoms are not completely controlled.

Case 3

MC is a 62-year-old female with past medical history of Sjögren syndrome who is referred to your office for further management of her dry eye disease. She notes an almost constant feeling of burning, dryness, and foreign body sensation. She reports that she has been on Restasis twice a day bilaterally for the past year. Her rheumatologist started her on Plaquenil which she has taken for the last year and a half. She has had lower punctal plugs placed 3 months ago and believes they are still in place. She takes preservative-free artificial tears ten times per day but says the relief provided only lasts for a few, brief seconds when she uses them. She has missed multiple days of work this year due to her symptoms and is frustrated that nothing has helped her so far. She states that she is miserable and the problems are severely affecting her quality of life.

On examination, her best corrected visual acuity is 20/40 bilaterally with spectacle correction. Her intraocular pressures are 16 mmHg in both eyes. External exam and lids and lashes are unremarkable. Conjunctivas appear mildly injected. TBUT is 3 s. She has mucous standing in the inferior fornix. She has 3+ PEE on inferior cornea. Schirmer's testing without anesthesia is 4 mm, and her tear osmolarity is 320 mOsm/L.

What Additional Treatment Options Might you Offer to This Patient?

Patients with Sjögren syndrome clearly have inflammatory disease. In the presence of active inflammation, a short course of topical steroids, particularly if available in a preservative-free preparation, may be useful for reducing inflammation on the surface. In patients with more significant inflammation, a short course of oral steroids may also be highly effective. In general, the patient should be questioned about their systemic disease and whether it is active, in which case, a recommendation is made for the rheumatologist to increase the patient's systemic therapy.

The use of punctal occlusion in patients with severe disease is different from that in patients with more moderate disease (e.g., Case 2). In particular, in patient with severe disease, occluding a single punctum in each eye is unlikely to have any measurable effect, and instead total occlusion must be considered. This is best done as a trial of using plugs (dissolvable or permanent) in both upper and lower puncta and evaluating the patient response. If there is a positive clinical response, then cautery punctal occlusion of the puncta is offered as a more permanent solution (given the likelihood of plugs falling out with time).

Secretagogues like oral pilocarpine and cevimeline that mimic parasympathetic activity can be used in the treatment of dry eye disease, especially in patients with coexisting dry mouth such as SS.

Another good option for patients with level 3 disease is autologous serum tears. Autologous serum eye drops—produced by separating the liquid from the cellular components of a patient's own blood—are an important tool in dry eye disease, as the serum contains substances that support proliferation, differentiation, and maturation of the ocular surface epithelium. Additionally the serum contains immunomodulatory mediators. Availability of serum eye drops may vary depending on the availability of pharmacies that can compound them. Studies have shown improvement in symptoms and TBUT despite no changes in other objective measures [33]. In patients with AD-DED, we typically start with 20% serum (diluted in BSS). Patients are instructed to use the drops at least four to six times a day (or more) and to maintain the unopened bottles in the freezer and opened bottle in the fridge up to 1 week. While there has been some concern with the use of serum from patients with active systemic diseases, we have not experienced any complications in patients with Sjögren syndrome, and the only group where caution may need to be exercised are allergic diseases.

Recently, sutureless amniotic membranes, such as the ProKera and AmbioDisk, have been approved by the FDA for use in dry eye disease. Amniotic membranes have long been used in ophthalmology to promote healing of the ocular surface and to curb inflammation through downregulation of inflammatory cytokines. Patients with severe dry eye disease may benefit from a trial with an amniotic membrane. However, this treatment may represent only a temporizing measure, and it is unclear the duration of the benefit or how often the procedure would need to be repeated. Further studies are required to appraise its efficacy [34].

Scleral contact lenses such as PROSE lenses have been a revolutionary treatment for patients with severe dry eye disease and many other ocular conditions. Many patients endorse the comfort and the ability for the lenses to alleviate symptoms by recapitulating the ocular surface and housing medication and lubrication. However, the cost of the lenses may be prohibitive, and insurance coverage of lenses remains uncertain and inconsistent. Despite these barriers, the customizability of the lenses provides tremendous opportunity for improvement of patient quality of life, with improvements in symptoms, objective measures, and visual acuity in dry eye disease [35, 36]. PROSE lenses can also be utilized for debilitating diseases of the ocular surface such as graft-versus-host disease with substantial success [37].

You discuss her options and she decides to be fitted for scleral lenses. You arrange her an appointment to be fitted and advise her that the cost may be rather expensive and her insurance company may not pay for all of it. She explains that she is aware of the potential cost to her and proceeds with a scleral contact lens trial.

At a follow-up appointment later, she reports significant relief from wearing the lenses. Her symptoms during the day have dramatically improved. Her visual acuity is 20/20 OU with the lenses in place, and she has 1+ PEE on the inferior cornea. TBUT, Schirmer's testing, and tear osmolarity are unchanged. She expresses gratitude and is happy with her decision to try the lenses.

Acknowledgments *Financial Disclosures*: None of the authors have any financial disclosures regarding the contents discussed in this manuscript. *Conflict of Interest*: None of the authors have any conflicts of interest with the contents discussed in this manuscript.

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Source: Botsford B., Merali F.I., Yiu S.C. (2018) Aqueous-Deficient Dry Eye Disease: Evaluation and Management. In: Djalilian A. (eds) Ocular Surface Disease. Springer, Cham. https://doi.org/10.1007/978-3-319-15823-5_1.

2

Comorbid Psychiatric and Inflammatory Conditions in Dry Eye Disease

Nisreen Ezuddin, Sarah Avila, Anat Galor

Case #1: Ocular Surface Disease and Comorbid Psychiatric Conditions

VG is a 45-year-old white female evaluated in the clinic with complaints of increasing dryness and irritation in both eyes for the past several months. Symptoms are constant but vary in intensity over at time. On review of systems, the patient endorses fibromyalgia, depression, and anxiety, but she is not currently on any treatment. Her past medical history is otherwise unremarkable and she does not take any medications. The patient also denies tobacco, alcohol, or recreational drug use. Upon further questioning, she reports increased fatigue, weight gain, concentration problems, and significant sleep disruption over the past 3 weeks. She feels sad but denies suicidal or homicidal ideations.

On examination, her best-corrected visual acuity is 20/20 OU with normal intraocular pressures. Osmolarity testing (TearLab, San Diego) reveals a value of 293 mOsm/L OD and 295 mOsm/L OS. InflammaDry (RPS, Tampa) is negative with a blue band in the control center in both eyes. Evaluation of the external periocular skin is unremarkable. On slit lamp examination, the eyelid margins are clean, the sclera and conjunctiva are white and quiet, and the corneas are clear OU. On fluorescein examination, tear film breakup time (TFBUT) is 14 s and 15 s in the right and left eye, respectively. Tear lake is of normal volume. Schirmer's testing with anesthesia reveals 10 mm of wetting OD and 12 mm of wetting OS after 5 min. The remaining ocular examination is otherwise unremarkable.

A depression screening questionnaire (patient health questionnaire [PHQ-9]) was administered with a resulting score of 20 (range 0–27). This score corresponds to severe depression.

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What do These Findings Mean?

This patient has dry eye symptoms but a normal slit lamp exam. She also has concomitant symptoms of depression. The case of Mrs. G is not an uncommon one. Mental illness affects millions in the U.S.A. with anxiety disorders being the most common, affecting 40 million American adults over the age of 18, or 18% of the population. Anxiety and depression often coexist, and nearly half of patients with depression are also diagnosed with an anxiety disorder.

Symptoms of major depression include: (1) sad, depressed, or irritable mood, (2) loss of interest or pleasure, (3) significant sleep loss/gain; (4) sleep disruption, (5) loss of energy/fatigue nearly every single day, (6) significant appetite changes, (7) thoughts of death or dying, (8) concentration/decision-making difficulties, and (9) worthlessness or excessive guilt. A major depressive episode is characterized as lasting at least 2 weeks with clear changes from a previous state that interferes with life [1].

Patients with depression often present to other physicians with concomitant physical symptoms. In a study of 1146 primary care patients with major depression, 69% reported an unexplained physical symptom as their chief complaint (defined as symptoms outside of the classification for DSM-IV and ICD-10) [2]. Dry eye symptoms may be one of several physical complaints reported by patients with depression. The direction of the relationship, however, has not been established as it is known that chronic pain can lead to depression. As such, depression may occur in patients with chronic ocular symptoms, or, conversely, as above, dry eye symptoms may be one of many physical manifestations of depression.

Irrespective, if a patient presents with unexplained dry eye symptoms, a clinical screening for depression is reasonable. There are many different ways to screen for depression, and multiple factors need to be considered in choosing the appropriate screen. Firstly, the screening modality should have diagnostic accuracy in the population being screened, and, secondly, the screening measure should be feasible, which includes the number of questions, response format, literacy level, and time it takes to administer [39]. An important screening instrument used by psychiatrists is the Beck Depression Inventory (BDI-II), which is a 21-item questionnaire that monitors

Table 1: Comparison of depression screening instruments.

Instrument	Sensitivity (%)	Specificity (%)	Items	Response format	Literacy level	Time to administer (min)
BDI	90	79	21	Four statements of symptom severity per item	Easy	2–5
EDPS	82	86	10	Four frequency ratings	Easy	<2
GDS	81	78	15	Yes or no	Easy	2–5
PHQ-2	83	90	2	Four frequency ratings	Average	<1
PHQ-9	88	88	9	Five frequency ratings	Average	<2
WHO-5	93	64	5	Five frequency ratings	Easy	<2

BDI beck depression inventory, *EPDS* Edinburgh postnatal depression scale, *GDS* geriatric depression scale, *PHQ-2* patient health questionnaire-2, *PHQ-9* patient health questionnaire-9, *WHO-5* World Health Organization well-being index

for treatment response. The Beck Depression Inventory for Primary Care (BDI-PC) is an adaptation from the BDI-II, which includes a seven-item questionnaire with a cutoff of four points and has a sensitivity of 97% and specificity of 99% in identifying major depression in a primary care setting, as compared to the gold standard of the diagnostic interview [3, 4]. Table 1 shows a comparison of six different screening instruments used by physicians when screening for depression with the gold standard for comparison being a structured clinical interview.

Mrs. G also carried a diagnosis of fibromyalgia. Fibromyalgia is a disease characterized by centralized pain manifesting as multifocal pain in different body regions at different times, not fully explained by injury or inflammation. Interestingly, some patients with fibromyalgia have also been found to have small fiber neuropathy on biopsy [5]. While widespread musculoskeletal pain is a hallmark of fibromyalgia, insomnia, cognitive disturbances (e.g., forgetfulness, decreased concentration), headache, irritable bowel syndrome, depression [6], and dry eye symptoms have also been found to be more common in patients with fibromyalgia [7, 8].

How Often Does Depression Coexist with Dry Eye?

Depression has been found to coexist with dry eye in a number of different population-based studies from Beijing [9], Korea [10], and the Netherlands [11]. In two population-based cross-sectional studies involving 2113 patients from Beijing and Korea, the results showed that depression correlated with dry eye symptoms (gritty, sandy, burning, dry), but did not correspond with dry eye signs of tear breakup time (TBUT) or Schirmer's test score [9, 10]. In a study utilizing the US Veterans Affairs (VA) national database, both post-traumatic stress disorder [odds ratio (OR) 1.92, 95% confidence interval (CI) 1.91–1.94] and depression (OR 1.92, 95% CI 1.91–1.94) were found to increase the risk of a dry eye diagnosis. These findings were robust when considering the effect of age, gender, and concomitant use of antidepressants and anxiolytics [12]. Regarding pain, in a cross-sectional study of 425 patients, the frequency of dry eye symptoms was higher in the subset of study participants with a chronic pain syndrome (irritable bowel syndrome [IBS], chronic pelvic pain, or fibromyalgia) than without it, but ocular signs were no worse [11].

What are the Treatment Options in Comorbid Psychiatric and Pain Disorders?

Treatments for psychiatric conditions, like depression and anxiety, in patients with dry eyes are best approached by integrating pharmacological and nonpharmacological therapies (patient education, exercise therapy, cognitive behavioral therapy) while keeping the patient active in the process. These are based on the experiences in treating patients with fibromyalgia.

Pharmacologic Treatment

Pharmacologic treatments generally work by reducing the activity of excitatory neurotransmitters (such as glutamate) (e.g., pregabalin, gabapentin) or by increasing the activity of inhibitory neurotransmitters, such as norepinephrine, serotonin, and γ-aminobutyric acid or GABA (e.g.,

serotonin-norepinephrine reuptake inhibitors, which include duloxetine, milnacipran). After a diagnosis of depression or anxiety has been established, the next steps should be to determine whether treatment is needed or not, based on the clinical extent of severity, distress or impairment, and the patient's preference. If pharmacologic therapy is initiated, SSRIs or SNRIs are usually the first-line therapies given their reasonable side effect profile [13]. Table 2 gives a comparison of the SSRIs and SNRIs available in the treatment of depression and anxiety. After initiation of medication, changes in mood can be seen within 1–2 weeks [14–16].

Drugs listed in Table 2 have also been found effective in the treatment of fibromyalgia-associated pain and may be considered in patients with ocular surface pain. Currently, the best-studied medications include certain SNRIs (e.g., duloxetine and milnacipran), tricyclic antidepressants (e.g., amitriptyline), and anticonvulsants (e.g., gabapentin and pregabalin) [17–19]. Interestingly, other drugs frequently used to treat pain such as nonsteroidal anti-inflammatory drugs, opioids, and corticosteroids have not been shown effective in treating fibromyalgia pain. In fact, opioids have been shown to worsen fibromyalgia-related hyperalgesia and pain in other centralized pain states [20]. It is thought that the opioid system is hyperactive in fibromyalgia patients, possibly

Table 2: Pharmacologic treatment for fibromyalgia-associated pain/anxiety which may be considered for ocular surface patients.

Drug	Initial daily dose (oral, mg)	Daily dose range (oral)	Side effect profile/characteristics
Sertraline	25–50	50–150	Insomnia, agitation, GI upset, diarrhea
Fluoxetine	20	20–60	Insomnia, agitation, weight changes, takes weeks for effect
Paroxetine	20	20–50	Mild sedative, weakly anticholinergic
Citalopram	10	10–40	Can prolong QT interval, lower risk of insomnia and agitation
Duloxetine	30	60–120	Useful for treatment of comorbid pain conditions
Venlafaxine	75	75–225	Increased blood pressure (diastolic) and heart rate with increasing doses, greater risk of insomnia/agitation, useful for treatment of comorbid pain conditions
Buspirone	10 (divided doses)	10–60 (divided doses)	A nonbenzodiazepine anxiolytic, ineffective for comorbid major depression
Mirtazapine	15	15–60	Appetite stimulant, useful for anxiety with insomnia, sedating, atypical antidepressant
Quetiapine	25–50	50–300	Extrapyramidal symptoms, weight gain, metabolic side effects
Imipramine	75 (divided doses)	75–200 (divided doses)	Anticholinergic side effects, potential cardiotoxicity, TCA
Hydroxyzine	50 (bedtime)	25–50 TID	Anticholinergic side effects
Nortriptyline	10 (bedtime)	10–75	Anticholinergic side effects, dry mouth, dry eyes, somnolence, rarely tachycardia
Amitriptyline	5 (bedtime)	10–75	Anticholinergic side effects, dry mouth, dry eyes, somnolence, rarely tachycardia

explaining why opioids are ineffective at treating pain symptoms. As such, another promising treatment in fibromyalgia is low-dose naltrexone [21]. Naltrexone is thought to suppress microglial activity and, thereby, decreases the production of proinflammatory factors, such as cytokines, excitatory amino acids, and nitric oxide, which can cause hyperalgesia, fatigue, and other symptoms of fibromyalgia [22, 23]. In addition, trigger point injections may be beneficial in the treatment of fibromyalgia [24, 25].

Nonpharmacological Therapies

The best-studied nonpharmacological therapies are education, cognitive behavioral therapy, and exercise. For the initial treatment of unipolar major depression, numerous studies have shown that the efficacy of psychotherapy and pharmacologic treatment exceeds pharmacologic treatment alone. In fibromyalgia, other treatments include chiropractic manipulation, tai chi, yoga, acupuncture, and myofascial release therapy [26, 27]. Both transcutaneous and central neurostimulatory therapies have also been used to treat pain with some success in fibromyalgia [28, 29].

What is an Appropriate Management of this Patient?

In this patient, a multi-specialist approach is required. The ophthalmologist should work with the patient's primary care physician and encourage a referral to a mental health professional. Despite good cross-sectional data associating mental illness and dry eye, no longitudinal data exist to guide therapy in this case. For example, it is not known what effect treating chronic non-ocular pain and depression/anxiety will have on dry eye symptoms. As such, it is advisable for the ophthalmologist to provide local therapy to improve ocular surface health, as needed, and to work in conjunction with other specialties that can address the non-ocular conditions associated with dry eye.

Case #2: Aqueous Deficient Dry Eye in the Setting of Systemic Immune Disease

A 49-year-old female with history of inflammatory arthritis on hydroxychloroquine therapy presented to the eye clinic with complaints of decreased vision, burning, and redness in both eyes. She uses preservative-free artificial tears up to 6–8 times a day without relief. She states her symptoms are worse upon awakening and while working on the computer for her secretarial job. Past medical history is significant for back and joint pain, which have been well controlled with hydroxychloroquine and ibuprofen as needed. She is otherwise healthy and takes no other medications.

On examination, her best-corrected visual acuity is 20/25 OU with normal intraocular pressures. Osmolarity testing reveals a value of 308 mOsm/L OD and 315 mOsm/L OS. Evaluation of the external periocular skin shows no rashes or skin findings. On slit lamp examination, moderate telangiectasias are observed on her lower eyelid margins, and the

bulbar conjunctivas have mild hyperemia. On fluorescein examination, tear film breakup time (TFBUT) is 7 s and 9 s in the right and left eye, respectively. The patient has a decreased tear lake OU with 3+ punctate epithelial erosions in the inferior cornea. Schirmer's testing with anesthesia reveals 4 mm of wetting OD and 3 mm of wetting OS after 5 min. InflammaDry (RPS Technologies, Tampa) is positive with a moderate-strength band in both eyes. The remaining ocular examination is otherwise unremarkable.

What do these Findings Mean?

These examination findings suggest that the patient has aqueous deficient dry eye (DE). The definition of dry eye provided by the 2007 International Dry Eye Workshop (DEWS) report is "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear firm instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface" [30].

Given its multifactorial nature, no single test can identify all dry eye patients. A number of different diagnostic tests are used to evaluate different components of the ocular surface.

Tear Volume

Tear film volume can be examined using the slit lamp to observe the tear meniscus. An inferior tear meniscus height of less than 1 mm (in the absence of significant conjunctivochalasis obliterating the meniscus) suggests aqueous deficiency [30]. High-resolution anterior segment optical coherence tomography (OCT) has been more recently used to assess the inferior tear meniscus. The meniscus is first imaged with the machine, and the image is then used to calculate inferior tear meniscus volume [31].

A Schirmer's strip can be used, either with an anesthetic (a measure of basal secretion) or without an anesthetic (a measure of basal secretion and reflex tearing) [30, 32] to measure tear production. The Schirmer's test is performed by placing a small strip of filter paper on the margin of the lower eyelid, leaving it in place for 5 min and measuring the length of the strip that is wet with tears. A value greater than 10 mm of wetting is considered adequate, and several cutoff values for dry eye have been recommended including less than 5 or 8 mm of wetting [30]. This is variable however, and other clinicians use a value of 7 mm for the Schirmer's test without anesthetic and 3 mm for the Schirmer's test with anesthetic [29].

Tear Film Stability

Fluorescein TFBUT measures tear film stability after a fluorescein dye drop is instilled in the tear film. Observation through the slit lamp can show the early breakup of the fluorescein across the cornea, seen as a dark spot forming through the tear film [30, 31]. A TFBUT less than the normal 10 s is a sign of rapid tear film breakup, an indicator of tear instability. Any perturbation in the tear film, including aqueous tear deficiency or lipid deficiency (meibomian gland dysfunction), can lead to an abnormal tear breakup time.

Epithelial Disruption

Aqueous deficiency can also lead to disruption of the corneal and conjunctival epithelial cells. Evaluation of epithelial cell health is performed with the instillation of topical dyes, such as fluorescein and lissamine green [30, 32].

Osmolarity

Elevated tear film osmolarity is another finding that may be present in DE. Tear hyperosmolarity results from aqueous evaporation from the ocular surface, which can occur due to low tear volume, fast evaporation, or a combination of both. In general, a value of 305 mOsm/L or greater is considered mildly elevated and of 318 mOsm/L or greater as severely elevated as shown in a study by Versura *et al*., with high positive predictive values and likelihood ratios [33]. A difference of 10 mOsm/L between the eyes or after repeated measurements in the same eye also suggests a dysfunctional tear film as a stable osmolarity measurement over time is one metric of a healthy tear film.

Inflammation

Levels of inflammatory mediators, such as interferon gamma, interleukin 1, interleukin 17, and others, have been shown to correlate with the severity of ocular surface disease [34]. Up until recently, however, measurement of inflammatory mediators on the ocular surface has not been routinely available. InflammaDry is a new diagnostic test that can detect matrix metalloproteinase-9 (MMP-9) on the ocular surface. The InflammaDry test of MMP9 should be performed prior to administering ocular anesthetic, topical dyes, or the Schirmer's test. Tear samples are collected from the palpebral conjunctiva with the sample collector fleece until it glistens, indicating that the sampling fleece is saturated. The sampling fleece is then placed within the test cassette with the addition of buffer solution. Within 10 min, if there is an MMP-9 antibody-antigen interaction on the immunoassay test strip, the result window will read positive with two lines (one blue and the other one red). The test provides a qualitative (yes/no) response. According to the manufacturer, the intensity of the red line is directly related to the amount of MMP-9 present. The lower detection limit of the test is 40 ng/mL [35]. The intensity of the band probably does provide some quantitative information, but this has not been validated.

Our impression is that this patient has moderate to severe dry eyes in the setting of a rheumatologic disease (rheumatoid arthritis). This raises the suspicion for Sjögren's syndrome.

What Further Evaluation Would you Consider for the Patient?

Thus, the presence of Sjögren's syndrome should be evaluated for by eliciting a thorough clinical history, examining the ocular surface and oral mucosa, and obtaining a serology panel, including rheumatoid factor (RF) and antinuclear antibodies (ANAs) which are sensitive for autoimmune

diseases but not specific for Sjögren's. Within the ANA, a subset panel, the extractable nuclear antigens (ENAs), should be ordered to look for ANAs that bind to the ENAs, called anti-ENAs which include anti-RO (SS-A) and anti-La (SS-B) antibodies. Anti-RO (SS-A) and anti-La (SS-B) have a higher specificity for Sjögren's (positive in 70–95% and 60–90% of patients, respectively) [36]. Newer studies have identified additional antibodies in patients with SS to salivary gland protein 1 (SP-1), carbonic anhydrase 6 (CA6), and parotid secretory protein (PSP). Thus, SP-1, CA6, and PSP may be helpful in diagnosing other subsets of SS patients and perhaps aid in earlier diagnosis as recently shown in animal studies [37]. Negative serology, however, does not rule out SSs, and some patients with clinical evidence of SS may not have positive titers for these antibodies. In these cases, further testing may be necessary, including a salivary gland biopsy, performed by an ENT or oral surgeon.

Early diagnosis of SS is important given the risk of extraglandular manifestations, including cryoglobulinemia, vasculitis, anemia, leukopenia, and thrombocytopenia [38]. Patients with more severe sicca symptoms and those who develop extraglandular disease may need to be treated more aggressively with systemic medications such as hydroxychloroquine rather than the local measures used in those with milder sicca symptoms alone [39]. Although oral hydroxychloroquine has not been shown to improve dry eye, early institution of treatment is believed to improve salivary gland function [40] and may prevent progression to neoplastic transformation by modulating lymphoproliferation [41]. Rituximab has also been shown to be therapeutic in the treatment of severe extraglandular manifestations but also has not been shown to improve ocular symptoms so it is not recommended purely for ocular disease.

How Does Positive MMP Testing Affect Your Management of Patients with Ocular Surface Disease?

A positive MMP test provides objective evidence of inflammation on the ocular surface. Therefore, the patient should be given a trial of anti-inflammatory therapy. We typically start with a mild steroid such as loteprednol 0.05% or fluorometholone 0.01% (whenever available we prefer preservative-free steroids such as methylprednisolone) starting 2–3 times a day then tapering down to once a day by 1 month. If the patient feels improved on the steroids, then an anti-inflammatory agent such as cyclosporine 0.05% or lifitegrast is added while the steroids are tapered off or tapered down to once or twice a week.

Upon further questioning, the patient does report symptoms of dry mouth and a history of frequent dental caries. Serology comes back with high titers of +anti-RO and +anti-LA, and an official diagnosis of Sjögren's syndrome is made. She continued to use preservative-free artificial tears 6–8 times a day and has made lifestyle modifications such as sleeping with the fan off and increasing essential fatty acids in her diet. Given the inflammatory nature of her disease and the positive MMP testing, the patient was started on cyclosporine emulsion 0.05% BID OU and fluorometholone 0.01% BID for 1 month and then daily. The patient comes back to clinic after 2 months and reports that her symptoms are improved but not eliminated. Her steroids are tapered down to one or twice a week.

The patient is offered a choice of punctal occlusion or serum tears as the next step and prefers to go with serum tears first. Patient is started on autologous serum tears 20% four times a day, and 3 months later, she reported a significant improvement in her dry eye symptoms. In addition, corneal staining improved in both eyes. This patient continues to be monitored for ocular surface disease (while also being monitored for hydroxychloroquine toxicity on an yearly basis).

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Source: Ezuddin N., Avila S., Galor A. (2018) Comorbid Psychiatric and Inflammatory Conditions in Dry Eye Disease. In: Djalilian A. (eds) Ocular Surface Disease. Springer, Cham. https://doi.org/10.1007/978-3-319-15823-5_10.

3

Ocular Pharmacology of Tear Film, Dry Eye, and Allergic Conjunctivitis

Shilpa Gulati, Sandeep Jain

Abstract

Dry eye disease (DED) is "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear-film instability with potential damage to the ocular surface." DED comprises two etiologic categories: aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE). Diagnostic workup of DED should includes clinical history, symptom questionnaire, fluorescein TBUT, ocular surface staining grading, Schirmer's I/II, lid and meibomian pathology, meibomian expression, followed by other available tests. New diagnostic tests employ the Oculus Keratograph, which performs non-invasive tear-film analysis and a bulbar redness (BR). The TearLab Osmolarity Test enables rapid clinical evaluation of tear osmolarity. Lipiview is a recently developed diagnostic tool that uses interferometry to quantitatively evaluate tear-film thickness. In DED, epithelial and inflammatory cells produce a variety of inflammatory mediators. A stagnant tear film and decreased concentration of mucin result in the accumulation of inflammatory factors that can penetrate tight junctions and cause epithelial cell death. DED treatment algorithms are based on severity of clinical signs and symptoms, and disease etiology. Therapeutic approaches include lubricating artificial tears and immunomodulatory agents.

Keywords: Conjunctivitis, Diagnostics, Dry eye, Ocular surface, Tear film, Therapy

Tear Film Structure and Physiology

The tear film forms a layer approximately 3 μm thick and 3 μL in volume on the anterior conjunctival surface, and serves multiple functions including lubrication, antimicrobial protection,

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nutrition, maintenance of corneal transparency and surface stem cell population, removal of debris, and preservation of the quality of image projected to the retina. Estimates of tear turnover rate range between 0.12 and 1.47 μL/min (5–22.2%/min) (King-Smith *et al*. 2000; Dartt and Willcox 2013).

Tear film composition is dynamic, responding to environmental conditions in order to maintain ocular surface homeostasis. The film itself is an emulsion of three components: an outer lipid layer secreted by the meibomian, Zeis, and Moll glands; an intermediate aqueous layer secreted by the main and accessory lacrimal glands; and an inner mucin layer secreted by conjunctival goblet cells. The lipid layer is composed of a combination of low polarity lipids, such as wax and cholesterol esters, and high polarity lipids, such as triglycerides, free fatty acids, and phospholipids. The aqueous layer is composed of inorganic salts, bicarbonate ions, glucose, urea, enzymes, proteins, and glycoproteins. While traditionally understood as three separate and distinct layers, new studies suggest that the mucin and aqueous layers integrate to create a gradient of decreasing mucin concentration outwards to the aqueous layer (Dartt and Willcox 2013).

Dry Eye Disease

Dry eye disease (DED) is a complex symptomatic syndrome with myriad clinical variations, defined by the International Dry Eye WorkShop (DEWS) as "a multi-factorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear-film instability with potential damage to the ocular surface." (International Dry Eye Workshop [DEWS] Definition and Classification 2007) DED, synonymous with keratoconjunctivitis sicca (KCS), was subdivided by DEWS into two etiologic categories: aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE).

The pathophysiology of DED involves numerous pathways leading to a final common denominator of lacrimal functional unit (LFU) dysfunction. The LFU consists of the ocular surface (cornea, limbus, conjunctiva, conjunctival blood vessels), tears and their associated machinery (lacrimal glands, meibomian glands, goblet cells, epithelial cells, nasolacrimal duct), and relevant components of the nervous, endocrine, immune, and vascular systems. These elements preserve corneal clarity by maintaining lubrication, nutrition, and the surface stem cell population, while minimizing inflammation and microbial overgrowth.

Aqueous-deficient Dry Eye

Aqueous-deficient dry eye is caused by reduced lacrimal tear secretion, and can be further divided into two subgroups: Sjögren syndrome (SSDE) and non-Sjögren syndrome (non-SS) conditions. Sjögren syndrome is an autoimmune exocrinopathy in which activated T lymphocytes infiltrate lacrimal and salivary glands, causing apoptosis of acinar and ductular cells and subsequent dysfunction. Dry eye caused by gland hyposecretion is further worsened by a neurosecretory block, which may be caused by antibodies directed against muscarinic receptors of the glands, or inflammatory cytokines in tear film. Clinically, patients present with symptoms of both dry eye and dry

mouth (xerostomia); diagnosis can be aided by lab tests for autoantigens that are expressed by surface epithelial cells (anti-Ro and anti-La). Sjögren syndrome may occur as primary disease, but more often is secondary to a known autoimmune condition, most commonly systemic lupus erythematosus (SLE), polyarteritis nodosa, granulomatosis with polyangiomatosis, systemic sclerosis, primary biliary cirrhosis, or mixed connective tissue disease.

Non-SS dry eye can be divided into four categories of conditions: primary lacrimal gland deficiencies, secondary lacrimal gland deficiencies, obstruction of the lacrimal gland ducts, and reflex hyposecretion. Primary lacrimal gland deficiency is most commonly attributable to age-related dry eye (ARDE). As normal individuals age, glands are obstructed by the accumulation of ductal changes, including periductal fibrosis, interacinar fibrosis, paraductal blood vessel loss, and acinar cell atrophy. Other uncommon forms of primary lacrimal gland deficiency are: congenital alacrima, a rare cause of childhood DED; and familial dysautonomia (Riley Day syndrome), a progressive, autosomal recessive, neuronal developmental abnormality characterized by insensitivity to pain. In the latter condition, impaired sympathetic and parasympathetic lacrimal gland innervation and poor ocular surface sensation impede both emotional and reflex tearing (International Dry Eye Workshop [DEWS] Definition and Classification 2007).

Secondary lacrimal gland deficiencies may be associated with a number of systemic conditions in which the lacrimal gland is infiltrated by cells causing dysfunction: sarcoidosis (invasion by non-caseating granulomas); lymphoma (lymphomatous tissue); and AIDS (CD-8T lymphocytes). In graft vs. host disease (GvHD), fibrosis occurs ~6 months after transplantation with the invasion of periductal CD-4 and CD-8T cells, and antigen-presenting fibroblasts. Ablation or denervation of the lacrimal gland secondary to trauma or surgery may also cause DED.

Cicatrizing disorders that lead to lacrimal gland duct obstruction include: trachoma, which causes trichiasis, tarsal and conjunctival scarring, and meibomian gland dysfunction; cicatricial or mucous membrane pemphigoid, which causes severe conjunctival blistering; erythema multiforme, which is an acute and self-limited cutaneous disorder of variable etiology (drug, infection, malignancy) that may cause conjunctival scarring; Stevens–Johnson syndrome; and chemical and thermal burns.

Finally, any impairment of reflex hyposecretion can cause non-SS ADDE. Physiologic tearing occurs in response to a variety of stimuli: the cornea and lid margins are densely innervated by sensory branches of the trigeminal nerve, lacrimal and meibomian glands receive both parasympathetic and sympathetic innervation, and goblet cells have parasympathetic innervation. These pathways form the reflex arcs that control reflex tear secretion. However, surface sensory loss may lead to decreased reflex hyposecretion and blink rate (which causes dry eye through evaporative tear loss). Impaired corneal sensitivity is found in a multitude of common conditions including chronic contact lens wear, diabetes, refractive surgery, or neurotrophic keratitis (caused by HSV or HZV infection, or CN V damage); it can also occur secondary to systemic beta blockers, atropine, keratoplasty, or the limbal incision of extracapsular cataract surgery. Reflex motor block, or damage to CN VII, also leads to reflex hyposecretion since damage to postganglionic, parasympathetic fibers to the lacrimal gland decreases secretomotor function, and lagophthalmos due to incomplete lid closure increases evaporative loss of tears. Trauma may cause damage to these

pathways, as well as systemic medications including antihistamines, beta blockers, antispasmodics, diuretics, tricyclic antidepressants, and selective serotonin reuptake inhibitors.

Evaporative Dry Eye

Evaporative dry eye is characterized by a pathologically high level of tear evaporation and can be caused by internal conditions that affect lid structures or dynamics, or environmental factors and exposures. An example of an intrinsic cause is the reduced blink rate that accompanies driving, watching TV, reading, and computer work, leading to rapid evaporation. In contrast, environmental factors act directly on the external surface; common culprits include central heating, dry climate, air pollution, wind, chemical burns, and contact lens wear.

The most common cause of EDE is meibomian gland dysfunction (MGD), which is chronic inflammation of the eyelid margin posterior to the gray line that may be accompanied by squamous debris, terminal gland obstruction, and qualitative or quantitative changes in glandular secretion. MGD can be identified at slit lamp by morphologic features of duct orifice plugging, increased viscosity of excreta, or inability to express oil from the glands (Fig. 1). It can be evaluated with qualitative grading, meibography to measure the degree of gland dropout, or meibometry to quantify the amount of oil in the lid margin reservoir. Causes may be local (posterior blepharitis); systemic (such as acne rosacea, seborrhoeic dermatitis, atopic dermatitis); or syndromal (anhidrotic ectodermal dysplasia, ectrodactyly syndrome, Turner syndrome). Cicatricial MGD may occur secondary to local tissue damage such as with trauma, burn, pemphigoid, erythema multiforme, or vernal keratoconjunctivitis. Other causes of MGD include meibomian gland replacement, which occurs in distichiasis; gland deficiency, which may be congenital or acquired; or reversible gland atrophy, which is caused by isotretinoin acne treatment.

Intrinsic EDE causes include conditions that compromise lid apposition or decrease blink rate. For example, dry eye is common and often severe in thyroid eye disease, which causes lid retraction and proptosis leading to an increased palpebral fissure and lagophthalmos. The decline in blink rate that may accompany Parkinson's disease results from a decrease in the quantity of dopaminergic neurons in the substantia nigra, and is proportional to disease severity.

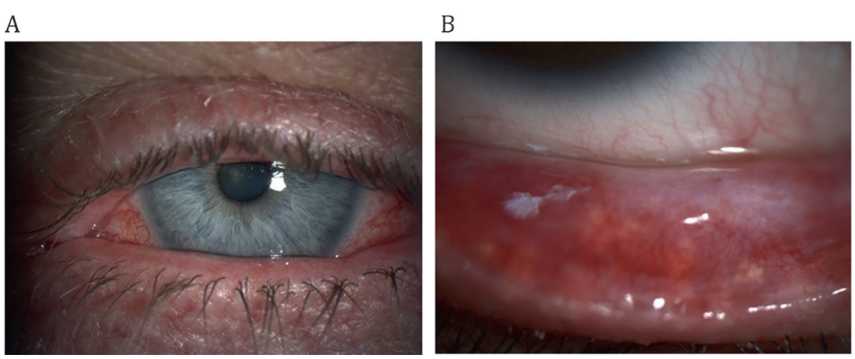

Fig. 1: (**A**) Lid margin telangiectasias, madarosis, and margin thickening and irregularity are characteristic of inflammatory conditions such as ocular rosacea. (**B**) Chronic severe inflammation can lead to conjunctival fibrosis.

In addition to increased tear evaporation time, infrequent blinking impairs clearance of lipid-contaminated mucin.

Tear film instability may be caused by indoor environmental factors, such as high temperature and low relative humidity (RH), as found in air-conditioned cars, offices, and airplane cabins. "Cool and dry" conditions are ideal, with recommended RH of about 40%. Likewise, outdoor exposure to sun, dust, and wind has been shown to worsen DED (Gayton 2009). These environmental exposures and trauma may also lead to corneal abnormalities, such as pterygium, which can disrupt the tear film and lead to symptoms of dry eye.

While women overall are more likely to have dry eye symptoms, hormonal studies suggest that sex hormone changes influence ocular surface conditions through both aqueous production and evaporative mechanisms: by impacting tear secretion, meibomian gland function, and conjunctival goblet cell density. This relationship is not fully understood but, in clinical studies, women taking oral contraceptives have been found to have significantly higher goblet cell density. Chronic reduction in androgen levels has been associated with meibomian gland dysfunction, the absence of anti-inflammatory cytokines such as transforming growth factor-beta (TGF-β), and the release of proinflammatory cytokines such as interleukins (IL-1β, IL-2), interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α). Accordingly, DED is more common in low-androgen conditions: post-menopause, primary ovarian failure, and autoimmune conditions. Furthermore, postmenopausal women on hormone-replacement therapy have a higher prevalence of DED, especially in women who are on estrogen only regimens (Gayton 2009; Peters and Colby 2013).

Epidemiology

Prevalence of dry eye increases with age, affecting 10% of adults age 30–60 and 15% of adults over age 65, and is more common among females (Weisenthal *et al.* 2015; Schaumberg *et al.* 2003). Based on data from large population based studies, the Women's Health Study (WHS) and the Physicians' Health Study (PHS), an estimated 3.23 million women and 1.68 million men in America over the age of 50 suffer from DED (International Dry Eye Workshop [DEWS] Epidemiology 2007).

The epidemiology of DED is limited by the different definitions employed by various studies. However, consistent evidence has been found to implicate several risk factors, including female sex, older age, postmenopausal estrogen therapy, a diet that low in Omega 3 essential fatty acids, a diet with a high ratio of Omega 6 to Omega 3 fatty acids, antihistamines, connective tissue disease, history of refractive surgery, vitamin A deficiency, androgen deficiency, hepatitis C infection, radiation therapy, and bone marrow transplantation (International Dry Eye Workshop [DEWS] Epidemiology 2007).

Symptom Analysis

Patients with DED present with a diversity of symptoms that include pain, dryness, grittiness, itching, redness, burning or stinging, foreign body sensation, and light sensitivity. As symptoms may persist or worsen over time, DED has been shown to negatively impact patients' quality of

life, both in general and vision-related. Given the variability of clinical tests, assessing DED symptoms in their entirety becomes fundamentally important to guide treatment decisions.

Hallek *et al*. at the University of Illinois at Chicago developed a four-domain symptom burden tool for comprehensive clinical evaluation of DED impact. Symptoms are classified into two main dimensions, sensory and reactive, and further subdivided into four domains: the sensory dimension is divided into symptom persistence and symptom intensity, and the reactive dimension is divided into activity interference and affective interference. A combination of visual analog, numerical, verbal descriptive, and verbal rating scales were then employed to calculate a numeric score for a patient's experience (Hallak *et al*. 2013).

In a cross-sectional 48-patient pilot study of this symptom burden assessment tool, the authors found that persistence of symptoms, and not intensity, was correlated with affective interference (or the "mood" of individuals). Because DED has been shown to correlate with anxiety and depression, the study concluded the need for an affective component to be added to standardized DED questionnaires, such as the Ocular Surface Disease Index (OSDI) (Li *et al*. 2011; Galor *et al*. 2012; Fernandez *et al*. 2013).

Authors also found that irrespective of clinical signs, the majority of patients reporting low symptom intensity received less aggressive treatments; management is governed by perceived severity. However, there is a well-established disconnect between signs and symptoms of DED (Mertzanis *et al*. 2005; Nichols *et al*. 2004; Johnson 2009). Traditional therapies for DED replace or conserve a patient's tears without correcting the underlying disease process. As a result the study concluded that clinicians need to objectively assess the type and severity of DED in order to effectively address the disease pathophysiology.

Diagnosis

Diagnostic tests to assess tear stability, ocular staining, and reflex tear flow, should be chosen based on patients' report of symptoms. Per DEWS the recommended order of tests is as follows: Clinical history, symptom questionnaire, fluorescein TBUT, ocular surface staining grading, Schirmer's I/II, lid and meibomian pathology, meibomian expression, followed by other available tests. The DEWS Diagnostic Methodology Subcommittee recommends the administration of structured symptomatology questionnaires to patients presenting with potential DED in order to use clinic time most efficiently. Several questionnaires have been validated and clinicians may choose one based on practical factors such as time, staff available to implement, and end use (International Dry Eye Workshop [DEWS] 2007).

Tear turnover may be evaluated by measuring tearfilm breakup time (TFBUT) in seconds. A standard amount of fluorescein is applied to the eye (as a drop, or by placing a fluorescein-impregnated strip that is wet with saline) initial instruction for the patient to blink in order to distribute the fluorescein. The patient should then be asked to open the eyes without blinking. Viewing under cobalt blue or yellow barrier light at the slit lamp, the clinician measures TFBUT: the interval between the last complete blink and the appearance of micelle, or disruption in the tear film. TFBUT cut-off for dry eye diagnosis is less than 10 s. While this test does not require

precision to identify extreme cases, it is subject to operator error; dye must be instilled delicately so that it doesn't elicit reflex tearing, and a standard amount of fluorescein should be placed in the eye (International Dry Eye Workshop (DEWS) 2007).

Epitheliopathy is a characteristic feature of DED, and surface integrity is quantified by grading of ocular surface staining with vital dyes. Most commonly used is hydrophilic sodium fluorescein dye, which diffuses into the corneal stroma to highlight areas of epithelial loss when viewed under cobalt blue light. In contrast, lissamine green (LG) adheres to epithelial cells that are devitalized or unprotected by mucin or glycocalyx; rose bengal (RB) adheres to these in addition to proliferating cells (Fig. 2). LG and RB dyes bear a number of advantages: both are poorly visible within the tear film so the dye in the tear film does not obscure the staining pattern (as with fluorescein, Fig. 2); and since these dyes do not diffuse into the substantia propria of the conjunctiva, there staining pattern lasts longer. While both are well visualized with the backdrop of a light colored iris, they are difficult to see against a darkly pigmented background. RB staining also carries the disadvantage of ocular toxicity, causing stinging and pain that are worse with photoactivation. The degree of staining is dose dependent, however, so instilling a smaller amount or concentration of dye will modify the result. Therefore this test is best performed after instillation of topical anesthetic, and should be followed with saline irrigation (International Dry Eye Workshop [DEWS] 2007).

For each ocular surface staining test, a saline moistened dye-impregnated strip is first used to instill dye on the inferior palpebral conjunctiva. After 15 s, corneal and conjunctival staining are graded by a slit lamp examination (cobalt blue filter is used for fluorescein dye, and rose filter is used for RB and LG). The 1995 National Eye Institute/Industry Workshop scale divides the cornea into 5 zones and the conjunctiva into 6 zones, and each zone is graded from 0 to 3 based on the density of punctate staining. The final staining score is the sum of the individual scores from all 11 zones. While a greatly simplified Oxford system has since been developed to evaluate ocular surface staining, the NEI scale is preferable because it isolates the visual axis in its own corneal zone (Lemp 1995).

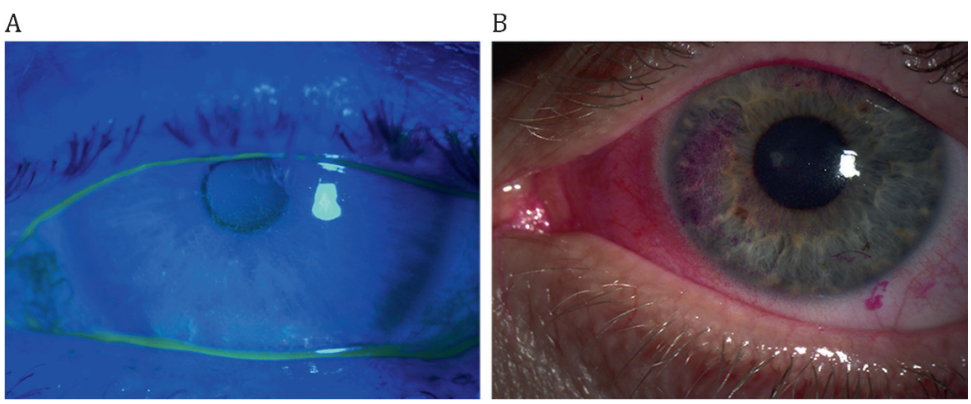

Fig. 2: (**A**) Sodium fluorescein dye stains devitalized epithelial cells, and highlights a narrow tear lake. (**B**) Rose bengal dye stains devitalized epithelial cells, those unprotected by mucin or glycocalyx, and proliferating cells; however, it carries the disadvantage of ocular surface toxicity.

Aqueous tear deficiency is best assessed with the Schirmer's test, in which standardized Schirmer's strips are bent at the notch and placed carefully over the lower lid margin near the temporal angle of the lids. Strips remain in place for 5 min while the patient keeps both eyes closed, and afterwards the wetting length is measured. The Schirmer's I test may be conducted with or without the application of topical anesthetic; the diagnostic cut-off for severe dry eye is generally considered 5 mm or less tear production. Schirmer's II is preceded by stimulation of nasal mucosa. Intrasubject variation invalidates comparison of results between individual patients, but same subject comparison can prove valuable despite day-to-day variation of results for a given patient (Whitcher *et al.* 2010).

New Diagnostics

A number of new diagnostic tests employ the Oculus Keratograph, which performs non-invasive tear film analysis (Fig. 3). The keratograph uses a Placido bowl with a camera aperture that has a fixation mark in the center. The device provides consistent illumination, allowing scanning of the exposed bulbar conjunctiva. The system generates a bulbar redness (BR) score automatically, which is based on the area percentage ratio between the vessels and the rest of the analyzed area. The BR range between 0.0 (0%) and 4.0 (40%, the maximum ratio) objectively evaluates ocular surface redness.

The same machine is also used to calculate non-invasive keratograph tear film breakup time (NIKBUT); this is a more objective measure of tear film stability than a slit lamp evaluation of TFBUT, and does not require application of fluorescein. The keratograph measures tear breakup time twice for each eye using infrared (IR) video and automatically generates two measures of

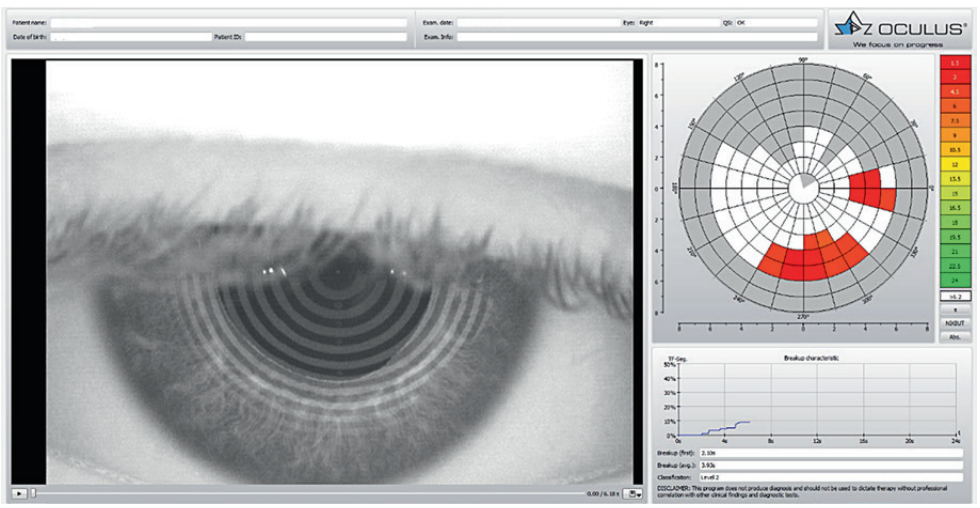

Fig. 3: The Oculus Keratograph calculates first TFBUT (time at first break up of tears) and average TFBUT (average time of all breakup incidents), as well as tear meniscus height (TMH) throughout the cornea.

output: NIKBUT-first (time at first break up of tears) and NIKBUT-average (average time of all breakup incidents).

Infrared images are also used to evaluate tear meniscus height (TMH), an element of tear film quality. The Oculus TMH tool uses an integrated ruler to measure TMH, which is graded perpendicular to the lid margin at the central point relative to the pupil center.

The failure of lacrimal tear secretion involved in ADDE causes tear film hyperosmolarity, and subsequent epithelial cell hyperosmolarity, which in turn initiates a cascade of inflammatory events involving MAP kinases, NFkB signaling pathways, cytokines IL-1 and TNF-alpha, and matrix metalloproteinase 9 (MMP-9, an endopeptidase involved in tissue remodeling). The presence of tear hyperosmolarity and MMP-9 in tear film are therefore valuable tools as they implicate an aqueous deficient etiology of DED (though it is not possible to differentiate between dysfunction of the lacrimal gland itself or other elements of the tear-production pathway).

The TearLab Osmolarity Test, FDA approved in 2009, enables rapid clinical evaluation of tear osmolarity. An abnormal salinity reflects a failure of homeostatic regulation, a key feature of DED; when left unchecked, hyperosmolar tears in early stage DED will lead to damage of the cornea and conjunctiva characteristic of late stage disease. The outcome is continuous: the higher the osmolarity, the more severe the dry eye. To perform the test, a Test Card is touched to the inferior tear meniscus to collect ~50 nL of tear fluid by passive capillary action. The machine then utilizes a temperature-corrected impedance measurement to provide an indirect assessment of osmolarity. One prospective clinical study evaluated the relationship between clinical metrics of DED (OSDI, TFBUT, surface staining, Schirmer's, meibomian scoring, tear osmolarity) with a composite of these scores; tear osmolarity was the only marker to demonstrate a linear relationship without significant scatter. This test is also benefitted by its objectivity, quantitative nature, and operator independence (Sullivan *et al*. 2010).

Lipiview is a recently developed diagnostic tool that uses interferometry to quantitatively evaluate tear film thickness (Fig. 4). Infrared and transillumination images created through dynamic illumination and adaptive transillumination allow clinicians to visualize eyelid morphology and detect structural changes suggesting gland dilation, atrophy, or drop out in severe disease (Hosaka *et al*. 2011).

Inflammatory markers in tears are also a new focus of diagnostic tests. For example, corneal endothelial cells produce endopeptidases, such as MMP-9, after desiccating stress; this promotes corneal extracellular matrix degradation and epithelial cell loss. InflammaDry is an FDA-approved clinical tool that measures MMP-9 protein in human tears. The test must be performed prior to instilling ocular anesthetic or performing Schirmer's testing. Tear fluid sample is collected by dabbing the sampling fleece on the inside of the patient's palpebral conjunctiva at least 6–8 times, and then rest against the conjunctiva for 5 s. Once this sample is immersed in a buffer solution for at least 20 s, the test cassette is laid flat for 10 min. The result, represented by indicator lines, is binary: a positive result reflects a concentration of MMP-9 > = 40 ng/mL, and a negative result reflects a concentration of MMP-9 <40 ng/mL.

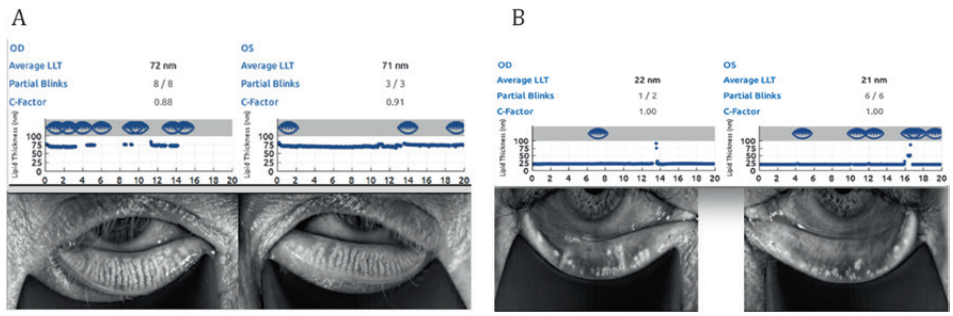

Fig. 4: Lipiview is a new diagnostic tool that uses dynamic infrared transillumination to visualize structural changes suggesting meibomian gland dilation, atrophy, or dropout. Images (**A**) and (**B**) demonstrate a visible contrast between normal gland structure and gland dropout, and a dramatic difference in lipid layer thickness (LLT).

Pathophysiology

The Innate and Adaptive Immune Systems

The innate immune system is the first line of defense in preventing microorganism invasion of the ocular surface. This system is composed of several nonspecific mechanical and chemical elements, including epithelial tight junctions and epithelial cell sloughing, reflex tearing, the barrier of closed eyelids, the conjunctival mucous membrane, mucins (glycosylated proteins produced by epithelial cells), anti-inflammatory factors (such as lactoferrin), proteolytic enzymes, pattern recognition receptors (PRPs), toll like receptors (TLRs), antimicrobial peptides (such as lysozyme, defensins, cathelicidins, and lipocalin), secreted phospholipase A2 (sPLA2), and secretory Immunoglobulin A (sIgA).

In the case of LFU dysfunction, epithelial and inflammatory cells produce a variety of inflammatory mediators that suppress T cell activation and inhibit complement-mediated tissue damage. Blinking, tear secretion, and tear drainage are all essential to flush away these inflammatory mediators from the ocular surface.

When they accumulate on the ocular surface, the proinflammatory cytokines IL-1 and IFN-γ cause squamous metaplasia of epithelial cells; IFN-γ inhibits goblet cell differentiation; intrinsic (stress-associated mitogen-activated protein kinase) and extrinsic (TNF and Fas/Fas ligand) pathways cause apoptosis of epithelial cells; and MMPs (such as MMP-9) promote corneal extracellular matrix degradation (Stevenson *et al.* 2012). Therefore, in the context of a stagnant tear film and decreased concentration of mucin, the resultant accumulation of inflammatory factors can penetrate tight junctions and cause epithelial cell death (Narayanan *et al.* 2013).

Once these primary protective mechanisms are infiltrated, the adaptive immune system is activated. Adaptive immunity is acquired through specific antigen exposures and is later triggered through re-exposure. Antigen-presenting cells (APCs), such as dendritic cells, elicit a response of T lymphocytes and antibody-producing B lymphocytes, to attack a recognized pathogen.

For example, exposure of corneal epithelial cells to elevated tear osmolarity activates apoptosis of the epithelial surface cells and stress-associated mitogen-activated protein kinases. These

in turn stimulate transcription factors (such as nuclear factor kB and activator protein 1) and the production of proinflammatory cytokines, chemokines, and MMPs. Cytokines and chemokines facilitate the maturation of APCs, which migrate to lymphoid tissue to expand the population of CD4+ helper T cell subtypes 1 and 17 (TH1 and TH17). These T cells travel to the ocular surface where TH 1 secretes IFN γ, and TH 17 secretes IL 17, which stimulates the production of MMPs. IFN γ and MMP-9 cause further damage to epithelial cells as noted above. The key to this proinflammatory cycle is the snowball effect (Stevenson *et al.* 2012).

External Stressors and Hyperosmolarity

Factors that disturb the homeostasis of the LFU ecosystem increase tear osmolarity. In a healthy state, the osmolarity of tear film is 296–302 mOsm/L; however, in patients with DED, this value rises to 316–360 mOsm/L. The hyperosmolar environment is caused by aqueous tear deficiency and/or increased evaporation of tears, and it stimulates a cascade of osmotic, mechanical, and inflammatory damage, as described above. It also stimulates formation of neutrophil extracellular traps (NET). Numerous neutrophils egress from circulation into tear film during ocular surface inflammation, and NETS on the ocular surface of patients with severe tear deficiency are associated with expression of type I interferon, plus inflammatory cytokines like interleukin-6 and tumor necrosis factor-alpha in ocular surface cells.

Tibrewal *et al.* recently reported that the amount of NETs released by neutrophils increased exponentially as hyperosmolarity increased, suggesting that NETs likely play a larger role in severe DED with greater hyperosmolarity (>350 mOsm/L) than mild dry eye with minimally elevated osmolarity. Furthermore, neutrophils were found to continue to release NETs, albeit in reduced amounts, even if the iso-osmolar milieu was restored (Tibrewal *et al.* 2014). The clinical implication of this finding is that although pulsed application of iso-osmolar or hypotonic artificial tear eye drops will intermittently reduce osmolarity, neutrophils will continue to release NETs once exposure to hyperosmolarity recurs.

Management

The development of pharmacological therapies for DED has been limited by our incomplete understanding of the mechanism, pathogenesis, and clinical manifestation of DED. Classification of DED by etiology is valuable in choosing a therapeutic approach because while ADDE and EDE often coexist and most treatments are effective for both types (such as artificial tears, cyclosporine, and steroid drops), some therapies are harmful if inappropriately used. For example, punctal plugs therapeutically increase tear retention time in ADDE, but in the presence of MGD they also increase ocular surface exposure to toxic inflammatory factors (Whitcher *et al.* 2010).

Stepwise Treatment

The International Task Force at Delphi in 2006 developed stepwise treatment algorithms based on severity of clinical signs and symptoms, and disease etiology. This was modified by the

International DEWS in 2007, which published a dry eye grading scheme that assigns a severity score of 1–4+ based on each of 9 diagnostic metrics: discomfort, severity and frequency; visual symptoms; conjunctival injection; conjunctival staining; corneal staining (severity/location); corneal/tear signs; lid/meibomian glands; TFBUT; and Schirmer's score.

The DEWS treatment scheme is based on severity. For level 1 it recommends education and counseling, environmental management, elimination of offending systemic medications, and preserved tear substitutes or allergy eye drops. If these are inadequate, level 2 treatment involves preservative-free tears, gels and ointments, steroids, cyclosporine A, secretagogues such as pilocarpine (now rarely used); and nutritional supplements. Level 3 treatment entails tetracycline, autologous serum tears, and punctal plugs (after control of inflammation). For refractory level 4 DED, they recommended topical vitamin A, contact lenses, acetylcysteine, and moisture goggles, or surgical treatment (such as tarsorrhaphy) (International Dry Eye Workshop [DEWS] Management and Therapy 2007).

Prior to pharmacologic therapies, clinicians should consider risk factor modification, such as: smoking cessation, home humidifier use, diet modification to increase consumption of Omega three fatty acids, and discontinuation of systemic medications associated with dry eye (diuretics, antihistamines, anticholinergics, and psychotropics are most common).

Therapeutic Approaches

Lubricating artificial tears are hypotonic or isotonic buffered solutions, of neutral to slightly alkaline pH, containing electrolytes (including potassium to maintain corneal thickness, and bicarbonate to promote recovery of epithelial barrier function), a high colloidal osmolality (such as in glycerin or erythritol, which counteract hyperosmolar tear film), and viscosity agents to enhance retention time. Viscosity in drop and ointment formulations is achieved with macromolecular complexes: short-acting preparations are often based on carboxymethyl cellulose, polyvinyl alcohol, polyethylene glycol, or hydroxymethyl cellulose; longer-acting ointments are based on carbomer gels or paraffin. Lubricant agents are distributed both over-the-counter and by prescription; though there have been no large, randomized controlled clinical trials to compare the many ocular lubricants on the market, this class of agents remains the mainstay of DED therapy.

While multi-dose artificial tears are mandated by the FDA to contain preservatives such as benzalkonium chloride (BAK) in order to inhibit microbial growth, these are toxic in high quantities (instillation more than 4–6 times/day). The cytotoxic damage they inflict on epithelial cell shape, junctions, and microvilli can cause epithelial cell necrosis; the effect increases with decreased tear secretion and turnover (as found in DED), high concentration of preservatives, and frequency of exposure. For more severe dry eye characterized by lacrimal hyposecretion requiring frequent administration of lubricants, punctal occlusion, or use of multiple drops that have preservative elements, preservative-free preparations in single-use vials are preferable.

Tears may also be substituted with biologically compatible drops, autologous serum tears, which are made from serum that is isolated from the cellular components of blood. To prepare, peripheral blood (20 mL) is taken from a patient, centrifuged to separate the serum, which is then diluted to 20% with sterile saline. The tears are stored in a bottle coated with protection from UV

light and must be stored in a freezer for 1 month only, to maintain the desired composition. Serum has an osmotic pressure (300 mOsm) and pH (7.2–7.5) nearly matching that of natural tears (302 mOsm and 7.4, respectively). While the exact mechanism of action is unknown, serum tears contain key ingredients of epidermal growth factor (EGF), vitamin A, TGF-beta, and fibronectin, which promote epithelial healing and are also found in natural tears (Tsubota and Yamada 1992). Similarly, serum has been shown to upregulate mucin production, and contains serum antiprotease which inhibits collagenases. The addition of these trophic components to the water and electrolytes found in traditional artificial tears has been demonstrated to effectively treat DED and persistent epithelial defects (PEDs), and improve TFBUT and vital dye staining when compared to artificial tears.

Immunomodulatory agents also play a significant therapeutic role for DED. The most commonly used anti-inflammatory drop is topical cyclosporine A (CsA) 0.05%, as it has been shown to alleviate the symptoms of DED in about 50% of patients. CsA is a lipophilic peptide that binds with a group of proteins known as cyclophilins. By binding with cyclophilin A, which is found in the cytosol, CsA inhibits calcineurin, a protein phosphatase that dephosphorylates regulatory sites on transcription factors such as nuclear factor of activated T-lymphocytes (NFATs). Through this mechanism CsA selectively inhibits interleukin-2 (IL-2), which is required for the transcription of T cells, thereby suppressing a cell-mediated immune response and interrupting inflammatory cytokine production. However, since the T cell life span can last 110–180 days, CsA may take several months to take effect and a short course of topical steroids may be prescribed at the outset of treatment. CsA also binds to cyclophilin D to block the opening of the mitochondrial permeability transition pore (MPTP), thereby inhibiting epithelial cell apoptosis. With long-term use topical CsA increases tear production and goblet cell density. Commercially distributed as Restasis, CsA 0.05% is packaged without preservatives in single-use vials and twice daily dosing (Hessen and Akpek 2014).

Clinically, pulsed use of corticosteroid drops are often used off label for DED as they have been shown to improve the efficacy of artificial tears or punctal plugs alone. Corticosteroids have multiple mechanisms of action. They increase synthesis of lipocortin A, which suppresses phospholipase A2, an early step in the inflammatory cascade. Prostaglandin synthesis is halted at the levels of phospholipase A2 and cyclooxygenase (COX-1 and COX-2), thereby inhibiting local leukocyte adhesion and chemotaxis, as well as systemic inflammatory responses such as vasodilation and vascular permeability. Steroids also inhibit nuclear factor-kB (NF-kB), a transcription factor that promotes synthesis of proinflammatory molecules, thereby stimulating lymphocyte apoptosis; likewise, they decrease the production of inflammatory mediators on a genomic level (Hessen and Akpek 2014). In murine models topical steroids protect the integrity of corneal epithelial tight junctions, prevent desquamation of epithelial cells, and decrease MMP-9 levels, thereby preserving barrier function (International Dry Eye Workshop [DEWS] Management and Therapy 2007). In humans, pulsed dosing of loteprednol 0.5% (an ester steroid) starting with use 4 times daily for 1 week, followed by a slow taper, has been shown to improve bulbar conjunctival hyperemia and central corneal fluorescein staining scores by over 25% (Pflugfelder *et al.* 2004). Loteprednol and fluorometholone, a ketone steroid, have also been found to convey lower risk of elevated intraocular pressure when compared to other ketone steroid drops, prednisolone and dexamethasone.

In the case of artificial tears, cyclosporine and steroid drops, innate and active immune protection against microbial invasion may be compromised. For example, the antimicrobial peptides of the innate immune system lose their ability to kill *Pseudomonas aeruginosa* in the presence of carboxymethyl cellulose solutions in vitro. Cyclosporine has been found, in vitro, to inhibit the production of cytokines involved in wound healing, and increase susceptibility of epithelial cells to viral infection by reducing interleukin production; in human corneal epithelial cells, it has been shown to inhibit cell proliferation (Narayanan *et al*. 2013). Despite the potential drawbacks these agents remain the mainstay of treating DED.

In cases of meibomian gland dysfunction, the goal of all treatments is to improve the flow of meibom secretions, and a stepwise approach to treatment is employed to minimize antibiotic exposure. Warm compresses are used to dilate meibomian gland orifices, lid scrubs exfoliate debris from the lid margin, and lid massages coax secretions from inspissated glands, all in order to clear the pathway for oil flow. Washing the lid margin with dilute soap also decreases bacterial colonization, which has been shown to inhibit conjunctival goblet cell proliferation and increase the breakdown of meibomian lipid (International Dry Eye Workshop [DEWS] Management and Therapy 2007; Gilbard 2005). While these are valuable and proven tools for mild to moderate DED, more severe disease that is resistant to treatment may merit antibiotic therapy. Oral tetracyclines are commonly used to treat DED given their dual impact of broad spectrum antibacterial prophylaxis (though only minocycline and doxycycline are able to reach an effective concentration on the ocular surface), and anti-inflammatory effect, achieved through reduction of MMPs, IL-1α and TNF-α (Narayanan *et al*. 2013). A new approach to treatment of MGD is LipiFlow, in-office thermodynamic treatment for obstructed meibomian glands. The device is a disposable apparatus that is inserted under a patient's upper and lower eyelids; it transfers heat to the palpebral conjunctiva while applying graded, pulsatile pressure to the outer eyelid to express meibom from glands (Finis *et al*. 2014; Lane *et al*. 2012).

For both ADDE and EDE, non-pharmacologic tear preservation can be achieved through a longer-acting approach, such as punctal occlusion, or a physical barrier, such as moisture chamber spectacles and contact lenses. Punctal plugs act by increasing longevity of tears in the conjunctival sac. Plugs are dumbbell-shaped, with a wide collar that rests at the puncta, a narrow segment that extends into the canaliculus, and a bulb at the end to anchor the plug internally. Temporary plugs are absorbable, made of collagen and lasting a couple months; these are often used to determine if a more permanent plug would be an effective treatment. In contrast, semi-permanent plugs are made of silicone or polymers. The complications of the procedure are few: excessive tearing (usually only if the upper and lower punctum are both occluded), development of a pyogenic granuloma, canaliculitis, or dacryocystitis. Tear retention is also the goal of moisture chamber spectacles, or contact lenses (such as silicone rubber lenses and rigid gas permeable scleral lenses) (International Dry Eye Workshop [DEWS] Management and Therapy 2007).

Allergic Conjunctivitis

As atopic diseases became more prevalent in the latter half of the twentieth century, so has allergic conjunctivitis (AC), which is estimated to impact up to 40% of the U.S. population

(Singh *et al*. 2010). AC encompasses several distinct conditions: seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis.

Diagnosis of DES requires differentiation from other common ocular surface inflammatory conditions. Because patients often find it difficult to characterize their discomfort, a nuanced history of symptoms can help elucidate whether the quality of pain is "burning" (more typical of DES) or "itching" (more specific for AC).

In SAC and PAC, allergens interact with IgE bound to sensitized mast cells, causing cross-linking of IgE at the mast cell membrane with subsequent degranulation and release of histamine, tryptase, prostaglandins, and leukotrienes. This early phase reaction lasts 20–30 min.

Mast cell degranulation also induces a late phase reaction by activating vascular endothelial cells that promote expression of chemokine and adhesion molecules, including monocytes chemotactic protein-1 (MCP-1), intracellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM), p-Selectin, and chemotactic factors IL-8 and eotaxin. These mediators recruit activated inflammatory cells (eosinophils, neutrophils, and T lymphocytes) to the conjunctiva. This late phase reaction is prolonged and plays a role in more severe forms of AC, with clinical manifestations of conjunctival injection, itching, chemosis, and conjunctival papillae found on exam (Bonini *et al*. 2009).

Because the conjunctiva has direct exposure to the environment and an abundant vascular supply to deliver immune mediators, SAC and PAC are common conditions that affect people of all ages. Seasonal allergies account for nearly 90% of all AC, and the most common allergens are airborne pollens that reach peak concentration during the spring and summer. Perennial exposures such as dust mites and mold can also stimulate the same ocular surface response.

Atopic keratoconjunctivitis and vernal keratoconjunctivitis, in contrast, do not involve sensitization of immune mediators to specific environmental exposures and often involve the cornea as well (keratoconjunctivitis). TH2 lymphocytes are thought to play a role in the pathophysiology of these conditions by producing inflammatory cytokines IL-4 and IL-13, which are found in abundance in patients with AKC and VKC; this is a common pathway among allergic disorders.

Vernal keratoconjunctivitis is a chronic inflammatory condition, most commonly affecting males (2:1 ratio) in tropical climates, that is characterized by broad "cobblestone" papillae on the upper tarsal conjunctival surface, mucus discharge, severe itching, and photophobia. Eosinophilic infiltration of the cornea may lead to the development of a well-circumscribed sterile epithelial "shield ulcer" with underlying stromal opacification, that can cause scarring even after resolution. "Tranta's dots" are collections of necrotic eosinophils, neutrophils, and epithelial cells that are found in crypts along the limbus in active disease. Epithelial cells may also release toxic mediators that compound this injury with macroerosions and plaques.

An estimated 15–20% of the U.S. population has atopy, a genetic predisposition to developing a heightened immune response to common allergens. AKC is the ocular corollary of the atopic conditions of asthma and eczema, which are present in 95% and 87% of patients with AKC, respectively (Guglielmetti *et al*. 2010). A family history of atopy is often positive. The pathophysiology involves IgE-mediated chronic mast cell degranulation and TH1 and TH2 lymphocyte derived cytokines, which cause severe itching, chemosis, and redness, leading to conjunctival scarring and

atopic cataracts if uncontrolled. Like VKC, AKC patients may also have giant papillae and Tranta's dots, but AKC more commonly affects patients in their late teens through the 5th decade of life, while VKC usually resolves by age 20.

Diagnosis

Allergic conjunctivitis is a clinical diagnosis. Referral to an allergist is essential for systemic workup, including allergen skin testing (scratch test or intradermal injections) and in-vitro IgE antibody tests.

Treatment

Primary treatment of PAC involves allergen identification and avoidance. Cold compresses may provide symptomatic relief. The primary topical therapy for all types of AC is artificial tears, which mechanically protects and flushes the ocular surface of immune mediators.

Traditional topical pharmacologic therapy for allergic conjunctivitis includes mast cell stabilizers, H-1 receptor antagonists, and combination mast cell stabilizers with H-1 receptor antagonists, nonsteroidal anti-inflammatories (NSAIDs), and steroids. Mast cell stabilizers prevent degranulation (via an unclear mechanism) but require a loading dose before reaching effective concentration and therefore have a delayed effect. The pharmacology of antihistamines is correspondingly insufficient in resolving symptoms when used as monotherapy. Because these agents reversibly block only H-1 receptors, leaving other inflammatory mediators uninhibited, they provide rapid but only temporary symptomatic relief.

In the past decade multimodal agents have become the mainstay of therapy because they couple the effect of H1 antagonists and mast cell stabilizers with other anti-inflammatory mechanisms. For example, a broader anti-inflammatory effect is achieved with Azelastine, a selective second generation H1 receptor antagonist that blocks intercellular adhesion molecules (ICAMs), and Epinastine, which blocks H2 receptors and thereby reduces eyelid swelling.

If symptoms persist despite first line treatment supplemental agents may be added. NSAIDs inhibit cyclooxygenase, reducing conjunctival redness and itching mediated by prostaglandins D2 and E2. Corticosteroid drops more directly treat AC by antagonizing NFκB, TGF-β, and activating T-lymphocytes into TH2.

Severe cases require systemic therapy, such as oral antihistamines and less commonly intranasal corticosteroids, in complement to local treatment. Allergen-specific immunotherapy by subcutaneous injection (or sublingual administration) may benefit patients with detectable IgE antibodies to known allergens.

Bacterial Conjunctivitis

Conjunctivitis is a nonspecific term that describes inflammation of the conjunctiva which may be caused by a wide range of conditions. AC is the most common etiology, but bacterial, viral,

chemical, and toxic conjunctivitis also occur frequently and present with overlapping symptoms. Viral conjunctivitis occurs more frequently in the summer and is the most common cause of infectious conjunctivitis overall and among adults. Bacterial conjunctivitis (BC), which occurs more frequently in the winter, is the most common form among children (50–75% of cases) and the second most common cause in adults (Høvding 2008).

The nonspecific symptoms of chronic BC allow it to masquerade as DES or AC. In a cohort study of 184 culture-positive cases, 58% of patients reported itching, 65% burning, and 35% serous or no discharge. Three signs were found to be strongly predictive of bacterial etiology: bilateral mattering of the eyelids, lack of itching, and no prior history of conjunctivitis. Notably the type of discharge did not correlate with etiology (Rietveld *et al*. 2004).

Bacterial conjunctivitis may be secondary to a systemic condition, such as in gonorrhea, chlamydia, graft-versus-host disease, and Reiter syndrome. Local BC may be transmitted oculogenitally, contaminated fingers or fomites.

Bacterial conjunctivitis may be subdivided into hyperacute, acute, and chronic forms depending on severity and speed of onset. Hyperacute BC is distinguished by rapid onset, profuse purulent discharge, lid swelling, and decreased vision. It is most commonly caused by *Neisseria gonorrhoeae*, which is treated with intramuscular ceftriaxone. Testing for coexisting genital chlamydial infection is requisite as it is positive in 54% of men and 74% of women (Azari and Barney 2013).

In contrast, acute BC lasts a little over a week and is characterized by conjunctival injection, mucopurulent discharge, and ocular discomfort. In adults the most common isolated pathogens are *Staph aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, while in children the most common culprits are *H. influenzae*, *S. pneumoniae*, and *Moraxella catarrhalis*.

Chronic BC presents similarly but lasts more than 4 weeks. Its most common pathogens are *S. aureus*, *Moraxella lacunata*, and enterics (Azari and Barney 2013).

Diagnosis

Practitioners should maintain a high degree of suspicion when contact lens wearers present with symptoms of conjunctivitis because this population is more likely to develop conjunctivitis caused by Gram-negative pathogens. Slit lamp exam should include a thorough evaluation of corneal integrity and the tarsal conjunctiva. Papillary and membranous conjunctivitis suggest a bacterial cause. If there is mucus discharge, it should be cultured to test for both viral and bacterial growth.

Treatment

A Cochrane meta-analysis that reviewed the treatment of suspected acute BC in 3,673 patients from 11 randomized clinical trials demonstrated that topical antibiotics improve the 5-day remission rate by only 31% compared with placebo. Many cases are self-limited, as clinical remission occurred by days 2–5 in 64% of those treated with placebo. Treatment with antibiotics was, however, associated with significantly better rates of clinical remission by days 2–5 (RR = 1.31), with possible benefit for late clinical remission (by days 6–10 RR = 1.27, with 95% CI = 1.00–1.61).

These data suggest a high degree of over treatment of acute infectious conjunctivitis with antibiotics. Notably, there were no serious adverse sight-threatening outcomes in any placebo group (Sheikh and Hurwitz 2001).

Clinically, topical antibiotics are indicated in patients with contact lens history, ocular surface diseases, corneal trauma, use of immunosuppressive medications, or history of ocular surgery. One large systematic review of 40 studies found that topical antibiotics had higher rates of clinical and microbiological remission in patients with positive bacterial culture, while only microbiological remission was significantly improved in patients with clinically suspected BC (Epling 2010). Patients with culture-positive results should be treated similarly, as well as those with suspicion for more aggressive pathogens that can penetrate an intact cornea (e.g., *N. gonorrhoeae*, *H. influenzae*, *Corynebacterium diptheriae*, and *Listeria monocytogenes*).

For adult patients with suspected but uncultured BC, who do not fall into a high risk group or have evidence of ulcerative keratitis, empiric treatment with broad spectrum topical antibiotics may be beneficial. Because the benefit of topical antibiotics is short lived and decreases the duration of symptoms without altering the outcome, some practitioners recommend antibiotics only if symptoms persist beyond 1–2 days. When conjunctivits is suspected to be bacterial but does not respond to appropriate therapy, chlamydial conjunctivitis should be tested for and empirically treated with a single dose of azithromycin, given its varied but often smoldering presentation and potential for scarring.

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4

The Microbiome and Ocular Surface Disease

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Abstract

Purpose of Review The human body lives in a symbiotic relationship with the bacteria, viruses, fungi, and protozoa that make up the microbiome. In this review, we discuss the compositions of the gut and ocular surface microbiomes in relationship to health and disease.
Recent Findings The gut microbiome is dominated by Firmicutes, whereas the ocular surface is dominated by Proteobacteria. The compositions of the microbiome are similar between individuals at the phyla level, but differ at the genus level. Alterations in the microbiome have been associated with disease. For example, ocular diseases such as uveitis, dry eye, and keratitis have been associated with gut dysbiosis. In addition, ocular surface dysbiosis has been reported in diseases including dry eye, blepharitis, keratitis, and diabetic retinopathy.
Summary Compositions of the gut and ocular surface microbiomes have been found to differ in disease states compared with controls. Further understanding of dysbiosis specific to a disease is needed to target these surfaces for therapeutic strategies.

Keywords Gut microbiome, Ocular surface disease, Dysbiosis, Gut-eye axis

Introduction

The human microbiome is comprised of the trillions of bacteria, viruses, and fungi that live in and on the human body. All of these microorganisms play an important role in impacting our physiology, both in health and disease. In 2008, the NIH initiated the Human Microbiome Project to characterize these communities of bacteria, viruses, and fungi from the phyla level down to the

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species level. Recent advances in bioinformatics and 16S rRNA sequencing have made this type of characterization possible by taking advantage of highly conserved genes with variables that allow bacterial genera distinction from one another [1, 2].

Initially, the Human Microbiome Project focused its attention on five main areas, including the gastrointestinal tract, skin, urogenital tract, oral mucosa, and nasal mucosa [3]. These efforts unveiled similar phyla but with differing relative abundances among healthy individuals. The healthy gut microbiome is dominated by Firmicutes and Bacteroidetes and also includes Actinobacteria and Proteobacteria [4, 5]. The oral mucosa is also mainly comprised of Firmicutes and Bacteroidetes, followed by Proteobacteria, Actinobacteria, Spirochetes, and Fusobacteria [6]. Most skin bacteria fall within the Actinobacteria phyla, followed by Firmicutes, Bacteroidetes, and Proteobacteria [7]. The nasal mucosa is predominantly composed of Firmicutes, followed by Proteobacteria, Actinobacteria, and Bacteroidetes [8].

Since the initial work by the Human Microbiome Project, the microbiomes at other sites have been explored. The ocular surface microbiome (OSM) has been found to be dominated by Proteobacteria, followed by Actinobacteria, Firmicutes, and Bacteroidetes [9•, 10, 11•, 12]. Interestingly, the OSM is paucibacterial compared with sites such as the gastrointestinal tract, with 0.06 bacteria per human conjunctival cell [13].

Sometimes dysbiosis, or change in the balance of resident bacteria relative to the community found in healthy individuals, may occur [14]. Several studies have found that various eye diseases are associated with gut and OSM dysbiosis. This review is aimed at summarizing this data and at discussing the relationship between the microbiome, eye health, and disease (Fig. 1). We additionally describe the manipulations of microbiomes in the treatment of eye disease.

Gut Microbiome

The gut microbiome plays a vital role in many physiological functions. Constituents of the microbiome digest food that is otherwise indigestible. For example, Bacteroidetes is useful in breaking down plant carbohydrates [15]. The microbiome is also involved in vitamin synthesis, such as in the case of *Bifidobacterium* which produces folate [16]. Furthermore, the microbiome is vital for immune development, including IgA production. For example, germ-free mice (mice without a native gut microbiome) had reduced numbers of IgA-producing plasma cells that quickly increased in number after gut colonization with bacteria [17]. In sum, the presence of a gut microbiome is essential for metabolic and immune activities.

In order to perform these important physiologic functions, a balanced composition is important. While in adults the phyla constituents are mostly consistent between individuals, there is greater interperson variation at the genus level. Typically, the gut microbiome is dominated by four phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria [4]. This was confirmed in two separate studies, one with 17 healthy individuals and another with 39 healthy individuals spanning six different nationalities. At the genus level however, there is greater variability. While the first study found *Faecalibacterium*, *Ruminococcus*, and *Eubacterium* as the most common genus [5], the second study reported *Bacteroides*, *Prevotella*, and *Ruminococcus* as the most abundant [18].

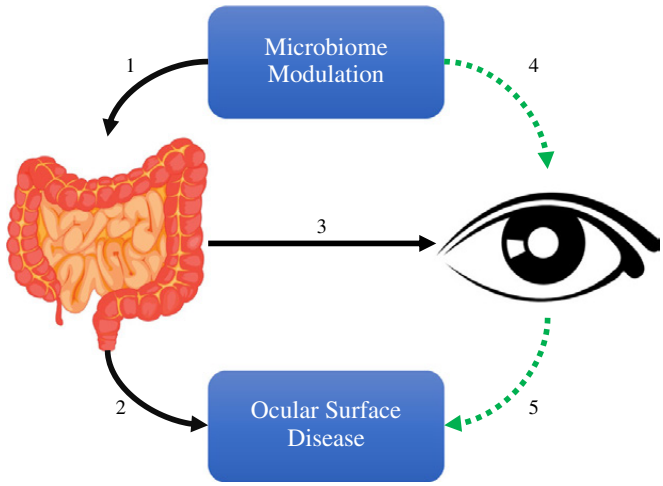

Fig. 1: Dysbiosis of the gut has been associated with ocular surface disease. Studies have shown that modulation of the gut microbiome (1) is helpful in treating ocular surface disease (2), possibly by changing the OSM (3). It is not fully understood, however, how manipulations of the OSM (4) affect ocular surface disease (5).

Many factors have been found to influence gut microbiome composition including age, genetics, and environment. In regard to age, the gut microbiome of 8 unrelated children and 1 twin pair was sampled at regular intervals in the first year of life. Earlier in life, there was greater variability between children. As they aged, the gut microbiome converged toward an "adult-like" composition with a predominance of Firmicutes and Bacteroidetes [19]. Genetics and environment have also been studied in relation to the gut microbiome. In a study of 326 children aged 0–17 years, differences were found in the microbiomes between individuals living in different countries. For example, a high representation of *Prevotella* was found in Malawians and Venezuelans, whereas *Bacteroides* was more abundant in the U.S. residents [20]. Taken together, this demonstrates that various factors affect the microbiome composition.

The Ocular Surface Microbiome

The gut is rich in bacteria with 10 gut bacterial cells for every one nucleated human cell [21]. The OSM has the opposite ratio as was demonstrated by a study of 107 healthy individuals. 16S rDNA analysis of conjunctival swabs revealed that the ocular surface contained 0.06 bacteria per human conjunctival cell, the buccal mucosa 12 bacteria per human cell, and the facial skin 16 bacteria per human cell [13]. One potential explanation for the paucibacterial nature of the OSM is the antimicrobial products found in tears, such as lysozyme, cationic peptides, and surfactant proteins [22].

In addition to the low number of bacteria on the ocular surface, the composition of the OSM differs from the gut microbiome. On the ocular surface, Proteobacteria dominates as opposed to Firmicutes in the gut. In a study involving 31 healthy adults, the relative abundance of Proteobacteria was 46.5%, Actinobacteria 33.9%, Firmicutes 15.5%, and Bacteroidetes 2.3% [9•]. Another study of 20 healthy adults characterized the abundance of Proteobacteria at 44.6%, followed by Firmicutes 36.3%, Actinobacteria 8.7%, and Bacteroidetes 3.0%. These studies indicate that, in general, the OSM composition is consistent between subjects on a phyla level [10]. At

the genus level, the first study reported that the OSM was comprised of *Corynebacterium* 28.2%, *Pseudomonas* 26.8%, and *Staphylococcus* 5.3% [9•], while the second study found the most abundant genera to be *Acinetobacter* 12.3%, *Aeribacillus* 11.3%, and *Acetobacter* 6.9% [10]. Collectively, these data suggest that similar to the gut, the phyla composition of the ocular surface is consistent between individuals, but genera composition varies.

The OSM has also been examined in relationship to its surrounding areas. In 20 healthy individuals, the ocular surface niche was found to be different than the eyelid and surrounding skin. Compared with the skin, the ocular surface had a higher relative abundance of Firmicutes and lower level of Actinobacteria and Bacteroidetes [10]. Differences in bacterial composition have also been reported from specific areas of the ocular surface itself. In a study of 23 healthy adults, the fornix and limbus were dominated by *Pseudomonas* (79.9%), whereas the conjunctiva showed a relatively low *Pseudomonas* abundance (6.3%) [11•]. Taken together, these data suggest that the OSM varies by location within the eye and surrounding tissues.

Age and gender have also been studied in regard to the OSM. In a study of 50 children (mean age 37 months), older children (> 6 months old) were found to have a higher OSM diversity as compared with children under 6 months of age. In older children, an enrichment of Actinobacteria and Proteobacteria and a reduction in Firmicutes were seen when compared with younger children (< 6 months) [23]. Another study comparing adults (mean age 57 years) and children (mean age 44 months) found a reduced abundance of *Streptococcus*, *Staphylococcus*, and *Brachybacterium* and an increased abundance of *Corynebacterium*, *Paracoccus*, and *Propionibacterium* in adults as compared with children [24•]. In both studies, no differences were identified by gender; however, other studies have reported gender-based differences. In a study involving 42 adults, females showed a β-diversity increase in *E. coli* and decrease in *P. acnes* and *S. epidermidis* compared with males [25]. Another study of 11 adults found females to have an increased abundance of *Acinetobacter* and *Enterobacteriaceae* and decreased abundance of *Anaerococcus* compared with males [26]. Taken together, the OSM composition may evolve with time, with an increase in diversity and appearance of different organisms in adulthood, and may be affected by gender.

Dysbiosis and Its Link to Eye Disease

In the gut, alterations in the bacterial profile have been linked to a variety of diseases. One such example is rheumatoid arthritis (RA), a disease with several potential eye manifestations. In one study of 42 individuals with RA and 10 controls, the presence of the phylum Euryarchaeota was an independent risk factor for RA and positively correlated with disease activity scores [27]. Another study found decreased gut microbial diversity in 40 RA patients compared with 32 healthy controls. In this study, the abundance of the phylum Actinobacteria and its genera *Eggerthella* was greater in RA compared with controls, while the abundance of *Faecalibacterium* was lower in RA than controls [28]. A pathophysiologic link has also been suggested between RA and *Prevotella*. In a study of 44 individuals with new-onset, untreated RA, expansion of *Prevotella* and depletion of *Bacteroides* were found compared with 28 healthy controls. These microbiome alterations were also accompanied by a lower abundance of genes

encoding for vitamin and nucleotide metabolizing enzymes in RA patients compared with controls. Of note, tetrahydrofolate (THF) biosynthetic enzymes such as dihydrofolate reductase (DHF) were reduced. This may explain why methotrexate, a DHF inhibitor and mainstay of RA treatment, may be effective in only a fraction of patients with RA. RA patients with a *Prevotella*-rich gut microbiome may respond better to methotrexate therapy than patients with a higher amount of DHF reductase-producing bacteria [29]. Interestingly, when treated with etanercept or methotrexate, the microbiome partially normalizes with an increased abundance of *Cyanobacteria* (producer of antiinflammatory metabolites) and decreased *Deltaproteobacteria* and *Clostridiaceae* (potential pathogens) [27].

Although studies identify different components of the dysbiotic microbiome in disease states, together the data suggests that gut dysbiosis is present in RA. Other diseases have also been associated with gut microbiome dysbiosis, including various ocular diseases.

Uveitis

Dysbiosis in the gut microbiome has been reported in uveitis. A study of 13 individuals with autoimmune or idiopathic uveitis compared with 13 controls found reduced abundances of *Faecalibacterium*, *Bacteroides*, *Lachnospira*, and *Ruminococcus* and increased abundances of *Prevotella* and *Streptococcus* in the gut of individuals with disease. The former are known to have an antiinflammatory effect via the production of short-chain fatty acids, while the latter are proinflammatory and pathogenic [30, 31]. A similar picture was seen in mice in which uveitis was induced by a retinal antigen (interphotoreceptor-binding protein) that elevated proinflammatory Th1 and Th17 levels, a reaction seen in autoimmune uveitis. When these mice were treated with oral antibiotics after the induction of uveitis, decreased abundances of phyla Firmicutes, Bacteroidetes, and Proteobacteria were noted compared with control animals that did not receive antibiotics after uveitis induction. The mice treated with antibiotics also had lower uveitis severity than controls, with lower levels of Th1 and Th17 levels and higher levels of Treg cells [32]. These data suggest that gut dysbiosis can modulate systemic inflammatory responses and affect the phenotype of inflammatory eye disease.

Dry Eye

Gut dysbiosis has also been described in Sjögren's dry eye. In a study of the gut microbiome in 10 individuals with Sjögren's, a greater abundance of the genera *Pseudobutyrivibrio*, *Escherichia/Shigella*, *Blautia*, and *Streptococcus* and a lower abundance of *Bacteroides*, *Parabacteroides*, *Faecalibacterium*, and *Prevotella* were observed compared with data from the Human Microbiome Project. Additionally, an inverse correlation was noted between gut microbial diversity and combined ocular and systemic disease severity [33]. Sjögren's relationship to the gut microbiome has been studied in the animal models as well. For example, CD25KO mice spontaneously develop dry eye and thus serve as a model of Sjögren's dry eye. Germ-free CD25KO mice were found to have a worse dry eye phenotype than CD25KO control mice, including increased lacrimal

gland inflammation, gland destruction, and IFN-γ-producing T cells in the lacrimal gland. Furthermore, $CD4^+$ T cells harvested from germ-free CD25KO mice and placed into immunodeficient mice cause a worse dry eye phenotype than $CD4^+$ T cells harvested and transplanted from control CD25KO mice. Interestingly, re-colonization of the gut microbiome in germ-free mice improved the dry eye phenotype, with an increase in goblet cell density, decreased lacrimal gland inflammation, decreased IFN-γ-producing T cells, and decreased corneal staining [34].

Similar findings have been reported in other dry eye models. In mice, desiccating stress was applied to the ocular surface through the use of a fan with or without scopolamine, an agent which causes dry eye features such as corneal staining and ocular surface inflammation. Interestingly, desiccating stress changed the gut microbiome, with an increase in Proteobacteria compared with nonstressed mice. The addition of antibiotics to the desiccating stress led to reductions in the phyla Bacteroidetes and Firmicutes and an increased Proteobacteria beyond desiccating stress alone. These gut microbiome changes were accompanied by a more severe dry eye phenotype and a reduction in IL-13/IL-17 [33], which stimulate goblet cell differentiation and mucus biosynthesis [35]. Another study comparing the effect of desiccating stress in germ-free mice with conventionally housed mice found that desiccating stress in germ-free mice resulted in a worse dry eye phenotype compared with controls, with reduced goblet cell numbers, increased lacrimal gland lymphocytic infiltration, and decreased epidermal growth factor levels in tears compared with controls [36•]. It is interesting to note that while in uveitis, antibiotics improved disease phenotype, and in dry eye, the opposite occurred, with antibiotics worsening the phenotype [35, 36•].

Taken together, these data support the importance of commensal gut bacteria in maintaining ocular surface health and the effect of dysbiosis on dry eye and ocular surface inflammation. These studies also set the foundation for modulating the gut microbiome as a potential therapeutic approach in dry eye.

Keratitis

Infectious keratitis has also been associated with gut dysbiosis. In one study, 19 individuals with bacterial keratitis were matched to 21 healthy controls. Individuals with keratitis had decreased gut diversity and decreased abundances of the phyla Firmicutes, Cyanobacteria, Elusimicrobia, and Tenericutes compared with controls. Concomitantly, the genera *Prevotella* and *Bacteroides*, which are proinflammatory and pathogenic, respectively, were more abundant in cases versus controls [37].

Similar findings have been described in the animal models. In a model of keratitis, Swiss Webster mice, which are normally resistant to *P. aeruginosa*, were more susceptible to developing *P. aeruginosa* keratitis when housed in a germ-free as opposed to a normal environment. Germ-free mice displayed higher bacterial burden, elevated proinflammatory cytokines, and higher pathology scores compared with controls. As in the dry eye model, when the gut of germ-free mice was recolonized with human or mouse microbiome, the mice became less susceptible to infection and had improved neutrophil function [38••].

Collectively, these data suggest the involvement of gut commensal bacteria in innate immune function and resistance to infection at distant sites (i.e., the eye). Furthermore, manipulation of the local microbiome was shown to modulate resistance to infection, with potential future therapeutic implications. However, it is important to note that one signature gut dysbiosis does not underlie all diseases. *Prevotella* was increased in uveitis and keratitis, but decreased in Sjögren's. *Bacteroides* and *Faecalibacterium* were reduced in uveitis and Sjögren's, but *Bacteroides* was increased in keratitis. Firmicutes was reduced in Sjögren's dry eye and keratitis, but antibiotics also reduced Firmicutes abundance and led to an improved uveitis phenotype. This highlights that complexity of linking compositional changes in the gut microbiome to disease.

Gut Microbiome Modulation as a Treatment for Eye Diseases?

There are several ways to modulate the gut microbiome. Dietary intake, for example, can modulate the composition of the gut microbiome. One study evaluated the gut microbiome in 11 healthy individuals who ate a meat-based diet for 5 days, followed by their normal diet for 1 month, and finally a plant-based diet for 5 days. Relative to a plant-based diet, a meat-based diet increased the abundance of bile-tolerant organisms such as *Alistipes*, *Bilophila*, and *Bacteroides* and decreased the abundance of Firmicutes such as *Roseburia*, *Eubacterium*, and *Ruminococcus*, known to digest plant polysaccharides [39]. Microbiome differences have also been shown with respect to diet in the mouse models. In one study, the gut microbiome of mice fed a Western diet (high in fat and simple carbohydrates, low in fiber) was compared with that of mice fed a high-fiber, plant-based diet. Mice fed a Western diet had reduced gut diversity, with decreased abundance of orders Clostriadiales and Bacteriodales (producers of antiinflammatory molecules like short-chain fatty acids) as compared with mice fed a high-fiber diet [40].

Probiotics can also impact gut microbiome composition [41]. In a study of 45 individuals with type II diabetes, oral *Lactobacillus* improved insulin sensitivity compared with controls receiving a placebo [42]. *Bacteroides fragilis* is another bacterium that has been used as a probiotic. In a mouse model of multiple sclerosis, oral treatment with polysaccharide A from *B. fragilis* delayed the onset and reduced the severity of multiple sclerosis when compared with untreated mice [43]. A similar signal has been seen in eye disease. In a mouse model of age-related macular degeneration, blue light-exposed mice fed a diet containing *Lactobacillus* maintained normal retinal thickness and a normal electroretinogram (ERG) compared with light-exposed mice fed a control diet which had a thinner retina and abnormal ERG [44•].

Fecal microbial transplant (FMT) is another avenue that has been used to modulate the gut microbiome. In humans, FMT has been applied to the study of graft versus host disease (GvHD), a condition associated with dry eye. In a study of four individuals with GvHD, FMT increased abundance of the beneficial bacteria *Lactobacillus*, *Bacteroides*, *Bifido bacterium*, and *Faecalibacterium* and concomitantly improved gastrointestinal symptoms such as defecation consistency and frequency in all patients. Interestingly, the gut microbiome of one patient who had a relapse of GvHD showed a high number of *E. coli* [45]. The abundance of *E. coli* has been directly correlated with GvHD severity in a mouse model. Antibiotic treatment decreased gut *E. coli* and improved GvHD severity compared with control mice not treated with antibiotics [46].

Taken together, these studies suggest that the gut microbiome can be modulated through diet, probiotics, and FMT. More studies are needed to understand which strategies are best to modulate specific diseases.

Ocular Surface Dysbiosis and Its Link to Eye Disease

Beyond the gut, alterations in the OSM have also been associated with ocular surface diseases including dry eye, blepharitis, keratitis, and diabetic retinopathy.

Dry Eye

Alterations in OSM composition have been found in the human and mouse models of dry eye. One study compared the OSM of the inferior conjunctiva in 15 individuals with Sjögren's dry eye versus 8 controls. The OSM of individuals with Sjögren's contained an increased abundance of Firmicutes and decreased abundance of Actinobacteria, Proteobacteria, and Bacteroidetes, although the differences were not statistically significant [33]. Another study evaluated conjunctival swabs from 29 females with Sjögren's dry eye as compared with 38 controls. Using the culture-based methods, individuals with dry eye grew fewer species compared with controls (mean 1.27 versus 1.51 species per subject, $p = 0.06$) [47]. On the other hand, another study collected conjunctival swabs from 91 individuals and found that those with dry eye (defined by symptoms, tear breakup time, goblet cell density, and meibomian gland assessment) were more likely to have a positive culture compared with controls (97%, $n = 30$ versus 75%, $n = 37$), but 16S rDNA PCR showed no statistically significant difference in the number of positive swabs [48].

Data for OSM disturbances has been more robust in the animal models of dry eye. Mice that are thrombospondin-1-deficient (TSP-$1^{-/-}$) spontaneously develop Sjögren-like dry eye as they age. One study compared conjunctival swabs from these mice with controls and found that TSP-$1^{-/-}$ mice develop an earlier colonization of the OSM with *S. aureus* and coagulase-negative *Streptococcus* species compared with controls [49]. To further accurately characterize the OSM changes in dry eye, more animal and human studies are needed.

Blepharitis

The OSM has also been studied with regard to anterior and posterior blepharitis [50]. In one study, 201 individuals with posterior blepharitis, defined as meibomian duct obstruction and abnormal meibum quality, were matched with 84 controls. Individuals with meibomian gland dysfunction (MGD) had a different bacterial profile cultured from meibum and the conjunctival fornix. Specifically, meibum from individuals with MGD was more frequently culture positive (aerobes 75.6% versus 36.9%, anaerobes 34.3% versus 10.7%, $p < 0.001$), with more frequent isolation of *S. epidermidis*, *S. lentus*, *S. aureus*, and *P. acnes* compared with controls. Similar findings were noted with the conjunctival fornix swabs [51]. Another study defining posterior blepharitis severity based on tear meniscus height, tear breakup time, tear foam, conjunctival injection,

corneal staining, eyelid margin qualities, and meibomian gland assessment found that individuals with severe posterior blepharitis had the highest frequency of culture positivity and the greatest variety of bacteria recovered meibum compared with controls and mild and moderate disease groups. Specifically, higher levels of *S. epidermidis* and *C. macginleyi* were found with increasing disease severity [52]. Another study of 157 individuals in New Zealand found coagulase-negative *Staphylococcus* as the most often cultured organism compared with healthy individuals, and *P. acnes* abundance was correlated with increased MGD severity [53].

The microbiome has also been examined in regard to anterior blepharitis. While one study found no significant difference in the OSM in individuals with anterior blepharitis compared with healthy individuals [53], another study reported the opposite. In a study of 7 individuals with anterior blepharitis defined as inflammation of the lid margin, tear samples found lower proportions of phyla Actinobacteria and genus *Propionibacterium*, as well as higher levels of phyla Proteobacteria, Firmicutes, and Cyanobacteria and genera *Staphylococcus*, *Streptophyta*, *Corynebacterium*, and *Enhydrobacter* compared with 4 controls [54]. Another study compared the bacterial growth of 117 patients with anterior blepharitis to 52 healthy controls. In the blepharitis group, *S. aureus*, *S. epidermidis*, and *P. acnes* were more prevalent compared with controls [55]. Although more studies using DNA-based technologies are needed for OSM characterization in blepharitis, these studies indicate a change in the OSM in blepharitis.

Keratitis

The OSM has been studied with regard to keratitis. One prospective study evaluated 236 contact lens wearers with microbial keratitis and found *P. aeruginosa* as the most common microorganism recovered by culture, followed by *Serratia* spp and *S. aureus*. Interestingly, *P. aeruginosa* was associated with patients living in warm, humid regions, whereas *Serratia* and *S. aureus* were more common in temperate regions [56].

Ocular Surface Microbiome dysbiosis has been reported in the mouse models of keratitis. The presence or absence of OSM dysbiosis has been shown to affect resistance to *P. aeruginosa*-induced keratitis. In a study using Swiss Webster mice (normally resistant to *P. aeruginosa*), mice were treated with topical antibiotics to deplete the OSM before ocular exposure to *P. aeruginosa*. These mice displayed higher numbers of *P. aeruginosa* at the ocular surface along with higher pathology scores compared with control mice that did not receive antibiotics [38••]. Another study found that manipulation of *Corynebacterium mastitidis*, a common skin bacterium, at the ocular surface affected susceptibility to keratitis. When *C. mastitidis* was depleted from the ocular surface with an antibody, mice became more susceptible to keratitis with *C. albicans* and *P. aeruginosa* [57••]. This study suggests an important role for OSM in modulating susceptibility to infection.

Diabetic Retinopathy

The OSM has also been studied in relationship to diabetes and its long-term complication, diabetic retinopathy. In a study of 9 individuals with type II diabetes with retinopathy,

OSM diversity was increased compared with 16 healthy controls. Specifically, Proteobacteria was increased in abundance while Firmicutes and Cyanobacteria were decreased compared with controls. At the genus level, the OSM in individuals with diabetic retinopathy showed an increased abundance of *Acinetobacter*, *Burkholderia*, *Rheinheimera*, and *Micrococcus* compared with controls [58]. Another study with 53 type II diabetics found a higher frequency of Gram-negative bacteria, including *E.coli* and *Klebsiella*, on the ocular surface as compared with 43 healthy controls [59]. Interestingly, contradictory findings have been reported in a Type I diabetic rat model. Type I diabetes was induced in mice via administration with streptozotocin, a diabetogenic agent that selectively destroys pancreatic beta cells. Conjunctival flora demonstrated a reduced diversity compared with control rats injected with saline. This was accompanied by a reduction in *Staphylococcus*, *Aerococcus*, and *Klebsiella* and an increase in *Enterococci*, *Kocuria*, *Enterobacter*, and *Proteus* on the ocular surface. This is important as species of *Staphylococcus* are normally present in healthy conjunctiva, whereas *Enterococci* are known to cause infection [60]. While diabetic retinopathy may take many years to develop [61], these data suggest that a change in bacteria at the ocular surface may be associated with the pathogenesis of diabetic retinopathy. Of note, it is important to realize that similar to the gut, there is not one signature OSM dysbiosis that underlies all ocular diseases.

Ocular Surface Microbiome Modulation as a Treatment for Eye Diseases?

As manipulation of the gut microbiome has been shown to affect ocular disease, manipulation of the OSM may impact eye disease as well. While there is less data to support this, one study tested the efficacy of probiotic eye drop treatment in 7 patients with vernal keratoconjunctivitis (VKC), a chronic allergic eye disease. Eye drops containing *Lactobacillus acidophilus* were administrated daily for 4 weeks, with improved symptoms of photophobia, itching, tearing, and hyperemia in six of the seven patients [62]. These results are promising; however, more studies are needed.

Conclusion

The gut microbiome has many physiological functions including digestion, immunity, and molecular synthesis. The role of the OSM is not fully understood; however, studies have shown it to aid in ocular surface immunity and susceptibility to infection. As such, both the gut and ocular surface microbiomes are likely important in maintaining a healthy state, whereas dysbiosis in both sites has been associated with disease. Several studies demonstrated the existence of a gut-eye axis where gut bacteria affect eye diseases including uveitis, dry eye, and keratitis. The animal models have demonstrated that the severity of eye disease can be impacted via gut microbiome manipulation. Less information is available on the link between OSM manipulation and eye disease. Future studies are needed to explore pathophysiologic mechanisms behind the noted associations and determine how this information can be used for therapeutic purposes.

Funding This study was supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Clinical Sciences Research EPID-006-15S (Dr. Galor), R01EY026174 (Dr. Galor), NIH Center Core Grant P30EY014801, and Research to Prevent Blindness Unrestricted Grant.

Compliance with Ethical Standards

Conflict of Interest Arjun Watane, Kara M. Cavuoto, Santanu Banerjee, and Anat Galor each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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Source: Watane, A., Cavuoto, K.M., Banerjee, S. *et al*. *Curr Ophthalmol Rep.* (2019) 7: 196. https://doi.org/10.1007/s40135-019-00217-w.

5

Optical Coherence Tomography for Ocular Surface and Corneal Diseases: a Review

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Abstract

The advent of optical coherence tomography (OCT) imaging has changed the way ophthalmologists image the ocular surface and anterior segment of the eye. Its ability to obtain dynamic, high and ultra-high resolution, cross-sectional images of the ocular surface and anterior segment in a noninvasive and rapid manner allows for ease of use. In this review, we focus on the use of anterior segment OCT, which provides an "optical biopsy" or in vivo imaging of various ocular surface and corneal pathologies, allowing the clinician to diagnose diseases otherwise not visualized by traditional methods. The utility of anterior segment OCT for various anterior segment pathologies is reviewed.

Keywords Anterior segment optical coherence tomography, Ocular surface imaging, Ocular surface lesions

Background

The rise of new imaging technologies has changed the way ophthalmologists assess the anterior and posterior segment of the eye. These imaging modalities have become instrumental adjuncts to clinical examination for the diagnosis and treatment of several ocular pathologies. There are many imaging modalities that can be employed particularly for the ocular surface and anterior segment including in vivo confocal microscopy, corneal topography, Scheimpflug tomography, high-resolution ultrasound biomicroscopy and optical coherence tomography (OCT) [1].

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Optical coherence tomography, which was initially developed for imaging the posterior segment, has shown great promise in systematically imaging the ocular surface and anterior segment from front to back (the tear film, conjunctiva, individual corneal layers, sclera, angle and lenticular structures). Anterior eye segment imaging using 830 nm light wavelength OCT was first demonstrated in 1994 [2]. However, blocked penetration of infrared light by the corneal sclera junction with resultant optical shadowing precluded visualization of trabecular iris angle structures. As such, introduction of transscleral anterior eye segment imaging was achieved by changing the light wavelength from 830 nm to 1310 nm in 2000. In 2005, the first commercially available anterior segment time domain OCT was released [3–6].

However, the transition from time-domain to spectral-domain devices, also known as Fourier-domain OCT, has allowed for faster scan speeds, greater tissue penetrance, and higher axial resolution images due to use of shorter wavelengths of light. Dynamic and rapid acquisition of images can be achieved with axial resolutions ranging from less than 5 μm (considered ultra-high resolution) to greater than 5 μm (considered high resolution). These images provide in vivo, cross-sectional views that elucidate the structural details of various conjunctival and corneal pathologies (Fig. 1) [7]. However, spectral domain OCT devices have the disadvantage of a reduced scan depth compared to time domain OCT machines due to shorter horizontal scan width [3]. More recently, swept-source OCT has emerged as the next advance in OCT technology, enabling simultaneous acquisition of numerous longitudinal and transverse scans to create 3-dimensional corneal, anterior segment and gonioscopic views [8]. There are several high-quality commercially available OCT machines as reviewed in Table 1 [7].

In contrast to the currently available devices, our institution has constructed a custom-built ultra-high resolution OCT machine that can acquire images of both high and ultra-high resolution, typically achieving axial image resolutions of 2 to 3 μm. Using a 3-module super-luminescent diode light source with a center wavelength of 840 μm, up to 24,000 A-scans can be generated to produce high-definition cross-sectional images of the area of interest. We routinely use this custom-built OCT at our institution to image both normal and abnormal ocular surface and anterior segment structures for clinical and research purposes [4, 9–13].

Importantly, OCT devices are noncontact and are well-tolerated by patients. The OCT machines can be used by most operators with varying levels of experience and the produced images can be easily interpreted by novice as well as experienced clinicians [14].

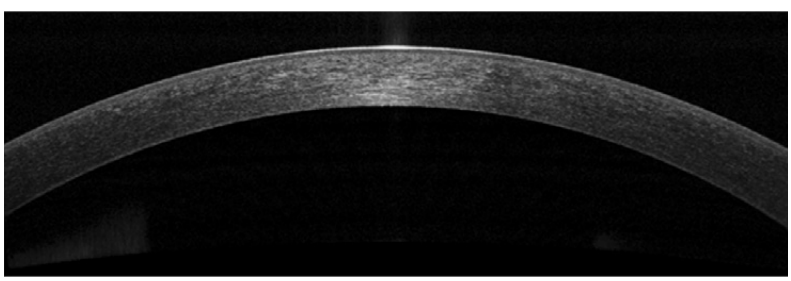

Fig. 1: AS-OCT of a normal tear film and cornea. AS-OCT displaying a normal tear film and cornea.

Table 1: Summary of characteristics of commercially available AS-OCT machines.

Instrument	Company	Measurement type	Approximate axial resolution	Scanning speed per minute
Stratus OCT	Carl Zeiss Meditec	Time-domain	10 μm	400 A scans
Visante OCT	Carl Zeiss Meditec	Time-domain	18 μm	2000 A scans
Slit-lamp OCT	Heidelberg	Time-domain	25 μm	2000 A scans
Spectralis OCT	Heidelberg	Spectral-domain	4–7 μm	40,000 A scans
Cirrus OCT	Carl Zeiss Meditec	Spectral-domain	5 μm	27,000 A scans
OCT SLO	Optos	Spectral-domain	< 6 μm	27,000 A scans
3D OCT 2000	Topcon	Spectral-domain	5–6 μm	50,000 A scans
RT Vue and iVue	Optovue	Spectral-domain	5 μm	26,000 A scans
Avanti	Optovue	Spectral-domain	~5 μm	70,000 A scans
SS-1000 CASIA	Tomey	Spectral-domain (swept source)	10 μm	30,000 A scans
Ultra high resolution OCT	Custom build device	Spectral-domain	~3 μm	24,000 to 26,000 A scans

In this review, we aim to discuss the various applications of anterior segment OCT (AS-OCT) for dystrophic, degenerative, and neoplastic ocular surface and corneal pathologies as well as provide recommendations for routine use of this beneficial technology in the diagnosis and management of these conditions.

Applications of Anterior Segment Optical Coherence Tomography

Diagnosis and Treatment of Keratoconus

Advances in anterior segment imaging have enabled the earlier detection and diagnosis of keratoconus and have allowed clinicians to better characterize the anterior and posterior corneal changes that can occur throughout disease progression (Fig. 2a and b). Imaging modalities commonly used for this condition include Schiempflug tomography, confocal microscopy and OCT [15].

Abou Shousha *et al.* [10] used our institution's custom-built ultra-high resolution OCT machine to image and map Bowman's layer, which is thought to play a crucial role in the pathogenesis of keratoconus. Topographic thickness maps were generated from AS-OCT images to calculate the thickness of Bowman's layer and specific Bowman's layer diagnostic indices were proposed. The study found characteristic localized thinning of the inferior cornea in corneas with keratoconus and that the average Bowman's layer thickness of the inferior cornea was significantly less than the average thickness measured on the superior cornea in corneas with keratoconus. Certain Bowman's layer indices also showed 100% sensitivity and specificity in the diagnosis of keratoconus and significantly correlated with average keratometry and astigmatic keratometry values [10]. This study showed that ultra high-resolution AS-OCT images can not only help characterize unique Bowman's layer changes in patients with keratoconus but also provide the means to calculate diagnostic indices that help clinicians more accurately determine this condition.

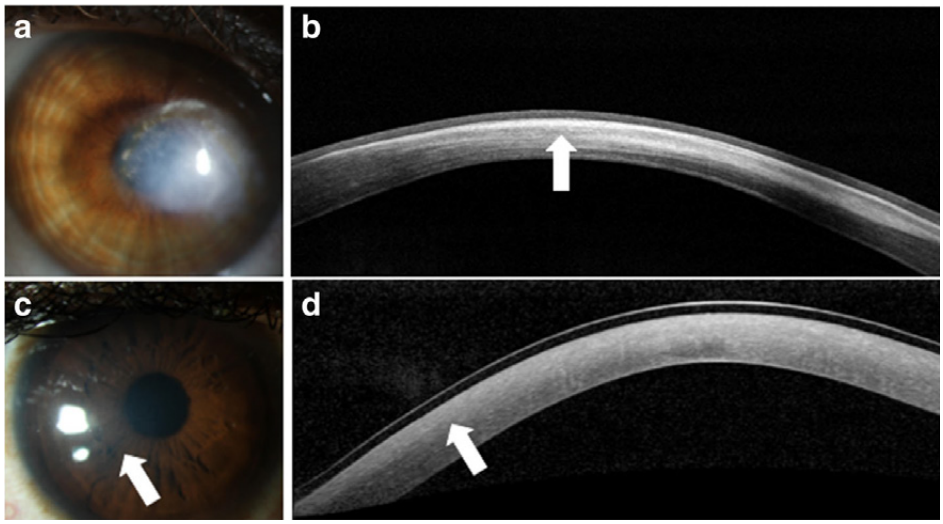

Fig. 2: Slit lamp photograph and AS-OCT of keratoconic corneas with corneal scarring. **a** Slit lamp photograph of central scarring in a cornea affected by keratoconus. **b** AS-OCT shows an area of anterior corneal scarring and thinning (*arrow*). **c** Slit lamp photograph of corneal haze three days after corneal collagen cross linking (*arrow*). **d** AS-OCT shows a subtle demarcation line in the area of corneal haze (*arrow*).

Importantly, newer commercially available swept source AS-OCT machines are able to scan wider corneal areas and can facilitate creating accurate topographic maps that include measurements from both the central and peripheral cornea and improve diagnostic capabilities [4, 16]. Spectral domain AS-OCT images can be used to characterize the corneal microarchitecture and regional epithelial thickness in patients with early keratoconus and post-operative corneal ectasia. Central epithelial thickness is often significantly thinner in eyes with ectasia and is overall more variable and irregular in ectatic eyes as compared with normal controls, which possibly contribute to changes in corneal topographic values [17]. Early changes in corneal epithelial and pachymetry maps derived from AS-OCT can also help in the early diagnosis of keratoconus in topographically normal eyes as well as in form fruste keratoconus [18, 19]. Additionally, AS-OCT may be used to evaluate epithelial thickness and stromal thinning at the cone and visualize the cornea and anterior chamber in cases of acute hydrops [20].

AS-OCT is useful in evaluating the effects of treatment for keratoconus, namely cross-linking. Recent papers have proposed the use of AS-OCT to identify corneal demarcation lines (defined by corneal edema and keratocyte apoptosis with changes in stromal reflectivity) to estimate the depth of penetration of different protocols of collagen cross-linking treatments (Fig. 2c and d) [21, 22]. Additional studies are however needed to further evaluate the utility of AS-OCT for gauging cross-linking treatment success. Furthermore, AS-OCT may be implemented to longitudinally evaluate changes in the geometric properties of keratoconic corneas after the insertion of intracorneal ring segments [23] (Fig. 3a) and also assess their position and depth in the cornea (Fig. 3b) [24].

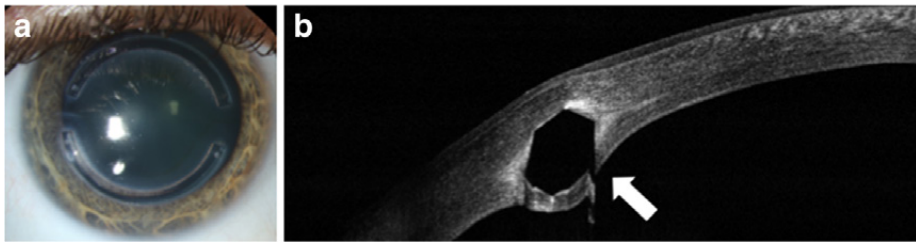

Fig. 3: Intrastromal corneal ring segments used in keratoconus. **a** Slit lamp photograph of an intrastromal corneal ring segment used for the treatment of keratoconus. **b** AS-OCT image captures the corneal intrastromal segment and helps assess its location and depth within the cornea (*arrow*).

Ocular Surface Lesions

Anterior segment-optical coherence tomography has shown great promise in the diagnosis and treatment of benign and malignant conjunctival and corneal pathologies. Ocular surface squamous neoplasia (OSSN) is one such pathology that has proven to be uniquely demonstrable on AS-OCT, particularly with devices that can acquire ultra-high resolution images [7]. Clinically, OSSN can present as papillary (Fig. 4a), gelatinous, opalescent or nodular lesions. Definitive diagnosis is traditionally made with incisional and in some cases, excisional biopsies and histopathological analyses. However, with the advent of AS-OCT, distinctive diagnostic features of OSSN

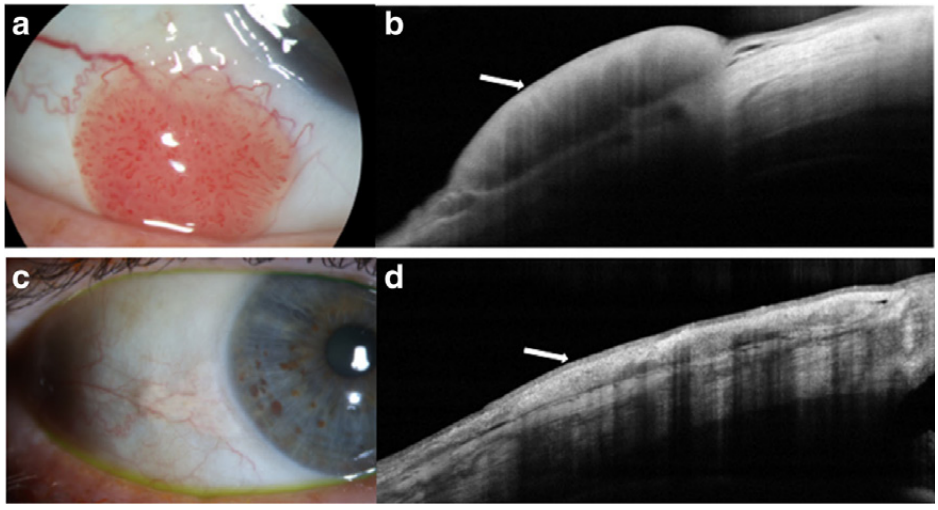

Fig. 4: Slit lamp photograph and AS-OCT of ocular surface squamous neoplasia pre and post treatment. **a** Slit lamp photograph of a papillomatous conjunctival lesion. **b** There is an abrupt transition from normal epithelium with thickened hyperreflective epithelium (*arrow*) on AS-OCT characteristic of ocular surface squamous neoplasia. **c** Slit lamp photograph showing complete resolution of the papillomatous conjunctival lesion after two cycles of 5-fluorouracil. **d** There is normalization of the conjunctival and corneal architecture (*arrow*) after two cycles of topical 5-fluorouracil on AS-OCT.

have been described that facilitate the diagnosis of OSSN with noninvasive methods. Notably, OSSN is an *epithelial* lesion; distinctive criteria on AS-OCT are a thickened, hyper-reflective epithelial layer with an abrupt transition from normal to abnormal epithelium (Fig. 4b) [7]. In cases of OSSN, these AS-OCT features resolve completely with normalization of the epithelium after successful medical therapy or surgical intervention (Fig. 4c and d) [9]. Moreover, AS-OCT is able to detect subclinical disease that often is not appreciated on slit-lamp examination [4]. As such, AS-OCT serves as a powerful tool for the non-invasive diagnosis of OSSN and can be used to determine the need for treatment initiation as well as monitoring of the disease course.

Other lesions that can be characterized by AS-OCT include conjunctival melanomas, lymphomas and amyloidosis [9]. Conjunctival melanomas clinically appear as thickened, raised, pigmented lesions with prominent feeder vessels and surrounding areas of melanosis, but they can also be amelanotic, often making the diagnosis challenging (Fig. 5a) [25]. AS-OCT images show a hyperreflective subepithelial lesion. The epithelium is normal to slightly thick layer of epithelium with variable hyperreflectivity of the basal epithelium (Fig. 5b), which suggests some involvement of the epithelium with atypical melanocytes. This imaging can help to rule in or rule out a pigmented OSSN versus melanoma. When OCT images do definitely rule out OSSN and suggest melanoma, immediate excisional biopsy can be performed. One drawback of these images is that thicker subepithelial lesions can exhibit significant shadowing, which often obscures the posterior limits of or subtle internal details of these subepithelial lesions.

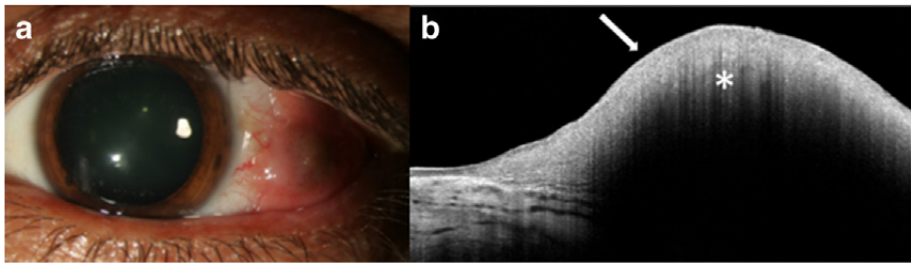

Fig. 5: Slit lamp photograph and AS-OCT of conjunctival melanoma. **a** Slit lamp photograph of a mixed amelanotic/pigmented conjunctival melanoma. **b** AS-OCT shows a hyperreflective, subepithelial lesion (*asterisk*) with thin but hyperreflective epithelium (*arrow*).

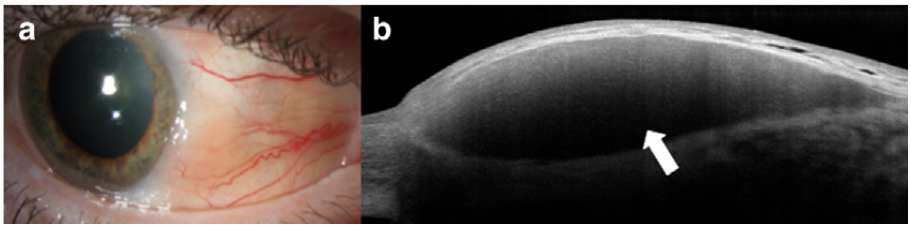

Fig. 6: Slit lamp photograph and AS-OCT of conjunctival lymphoma. **a** Slit lamp photograph of conjunctival lymphoma. **b** On AS-OCT, there is a homogeneous, dark, hyporeflective subepithelial lesion with smooth borders and overlying thin epithelium (*arrow*). The lesion contains monomorphic, stippled, *dot*-like infiltrates corresponding to the infiltration of monoclonal lymphocytes.

Conjunctival lymphomas clinically can present as focal salmon-patch masses, subconjunctival mobile masses or nodules (Fig. 6a) or as chronic follicular conjunctivitis. On AS-OCT, the condition is characterized by a normal layer of epithelium overlying homogeneous, dark, hyporeflective subepithelial lesions with smooth borders. The lesions can often contain monomorphic, stippled, dot-like infiltrates that correspond to the infiltration of monoclonal lymphocytes (Fig. 6b). For both melanomas and lymphomas, AS-OCT images do not always help the clinician obtain a definitive diagnosis as they do for OSSN, but can help guide the differential. Histopathologic analysis of tissue is needed for final confirmation.

Conjunctival amyloidosis can also clinically appear as a yellow or pink lesion on the conjunctiva, similar to lymphoma (Fig. 7a). However, on AS-OCT, images show normal epithelium overlying heterogeneous, dark lesions with irregular borders, as compared with the homogeneous and regular appearance of lymphomas. These *subepithelial* lesions often contain hyperreflective linear infiltrates corresponding with amyloid crystals (Fig. 7b). Once again, histopathology is still the gold standard for diagnosis and is often used for clarification of diagnosis in both primary acquired melanosis and conjunctival amyloidosis [9].

When considering benign lesions, AS-OCT can be used to characterize pterygia, conjunctival nevi or primary acquired melanosis. AS-OCT images of pterygia demonstrate a thin or normal layer of epithelium with varying levels of hyperreflectivity overlying a dense, hyperreflective, fibrillary subepithelial lesion that is between the corneal epithelium and Bowman's layer

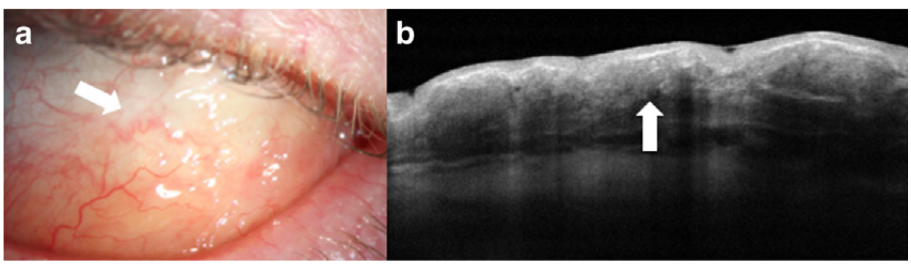

Fig. 7: Slit lamp photograph and AS-OCT of conjunctival amyloidosis. **a** Slit lamp photograph of conjunctival amyloidosis (*arrow*). **b** AS-OCT image of conjunctival amyloidosis showing a heterogeneous, dark subepithelial lesion with irregular borders containing hyper-reflective linear infiltrates that correspond to amyloid deposition (*arrow*).

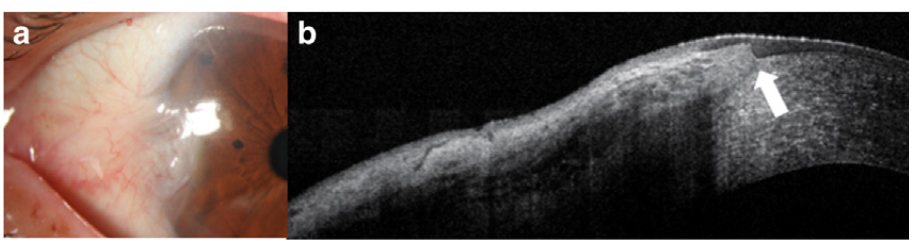

Fig. 8: Slit lamp photograph and AS-OCT of pterygium. **a** Slit lamp photograph of a pterygium. **b** AS-OCT image of the pterygium shows a dense, hyper-reflective, fibrillary subepithelial lesion that is between the corneal epithelium and Bowman's layer (*arrow*).

(Fig. 8a and b). In our experience, AS-OCT has been found to be very sensitive in distinguishing pterygia from OSSN. Several studies have shown that ultra high-resolution AS-OCT can reproducibly differentiate between pterygia and OSSN, namely by statistically significant differences in epithelial thickness and location of the primary lesion (epithelial for OSSN and subepithelial for pterygia) [11, 26].

Nevi, similar to melanomas, often have normal thickness or slightly thickened epithelium overlying a well-circumscribed subepithelial lesion, but unlike melanomas, nevi classically consist of cystic spaces (Fig. 9a), both clinically as well as on AS-OCT (Fig. 9b), which is suggestive of chronicity. Yet, the presence of cysts does not definitively rule out malignancy and a good clinical history and if needed, biopsy, is important to clarify the diagnosis. This technology is especially helpful in the diagnosis of amelanotic nevi often seen in children. In these cases, the cysts may not be clinically apparent, but the AS-OCT can easily allow them to be visualized to assist in the diagnosis. It is important to note that compound nevi can contain a portion of the lesion in the epithelium and substania propria in addition to the subepithelial space. Primary acquired melanosis on AS-OCT images is characterized by normal thickness but moderately hyperreflective basal epithelium with no invasion of the subepithelial space (Fig. 10a and b).

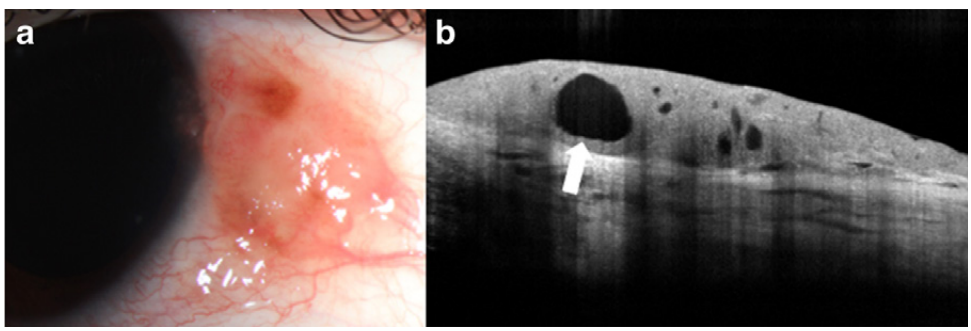

Fig. 9: Slit lamp photograph and AS-OCT of a conjunctival nevus. **a** Slit lamp photograph displaying a cystic nevus in a child. **b** On AS-OCT, this lesion is a well-circumscribed subepithelial lesion containing cystic spaces (*arrow*).

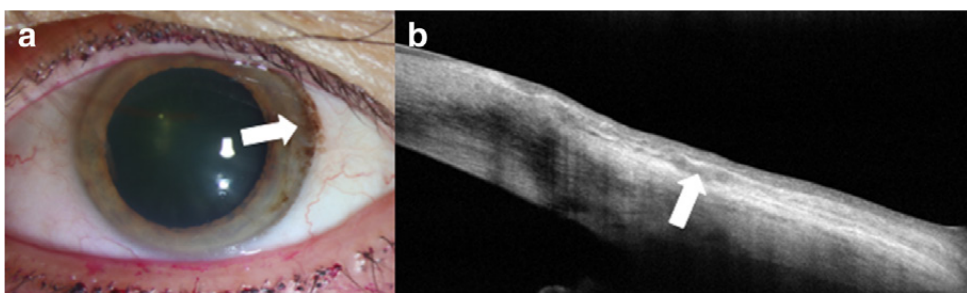

Fig. 10: Slit lamp photograph and AS-OCT of primary acquired melanosis. **a** Slit lamp photograph of primary acquired melanosis (*arrow*). **b** AS-OCT image shows areas of subepithelial reflectivity (*arrow*).

Corneal pathologies and surgical planning for corneal procedures

Anterior segment-optical coherence tomography can be utilized in the diagnosis and management of dry eye disease [5]. Studies have shown that the tear meniscus can be reduced in different dry eye populations including aqueous tear deficiency or thyroid-associated ophthalmopathy [27, 28]. In patients with dysregulated tear function, lower tear volume can correlate with corneal disease severity. On AS-OCT images, the tear meniscus is precisely measured, and with continuous measurements, the dynamics of the tear meniscus can be trended over time [4, 29, 30].

Anterior segment-optical coherence tomography can be used to image several dystrophic and degenerative conditions of the cornea. With our institution's custom-built AS-OCT, changes in corneal architecture are captured with two micron axial resolution images. The size, depth, and location of the corneal opacities or deposits can easily be assessed with this imaging modality.

Salzmann's nodular degeneration is characterized by localized areas of hyperreflective material that has replaced the anterior stroma and Bowman's layer underneath the normal epithelium (Fig. 11a and b). This condition can be identified by unique features on slit-lamp examination alone, but when clinical examination is insufficient in distinguishing it from other corneal degenerations, AS-OCT imaging can determine its location and along with diagnostic biopsy, can be extremely useful [12]. Band keratopathy is defined as the deposition of calcium in the Bowman's layer. On AS-OCT, this can be visualized as hyperreflective material at the level of the Bowman's layer causing shadowing underneath (Fig. 11c and d).

Other corneal dystrophies can also be imaged with AS-OCT. When considering epithelial dystrophies, AS-OCT images of anterior basement membrane dystrophy illustrate increased

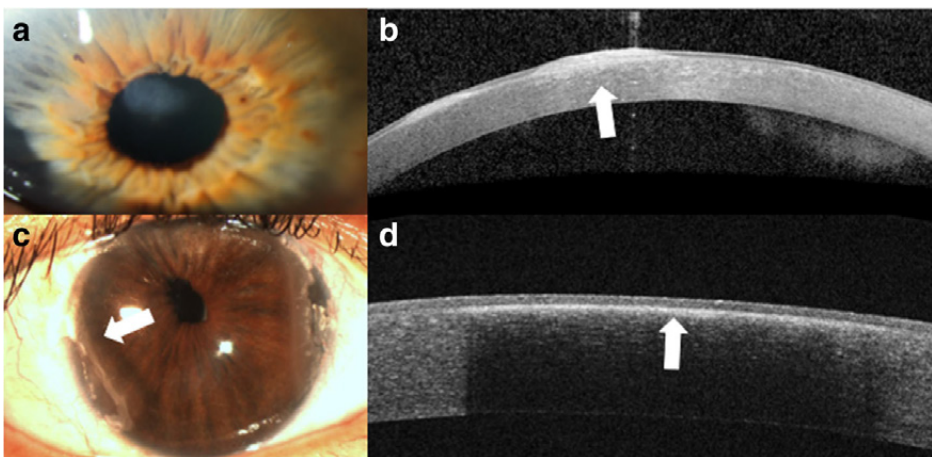

Fig. 11: Slit lamp photograph and AS-OCT of a Salzmann's nodule and band keratopathy. **a** Slit lamp photograph of a central Salzmann's nodule. **b** On AS-OCT, the nodule is seen as a localized area of hyperreflective material that has replaced the anterior stroma and Bowman's layer underneath normal epithelium (*arrow*). **c** Slit lamp photograph of band keratopathy in the peripheral cornea (*arrow*). **d** AS-OCT imaging shows a thin band of hyperreflectivity along Bowman's layer with underlying shadowing (*arrow*).

reflectivity of the epithelial basement membranes with areas of basement membrane duplication and intraepithelial hyporeflective cysts. In contrast, Meesmann's dystrophy is characterized by diffuse hyporeflective microcysts present throughout the epithelium. Dystrophies affecting Bowman's layer and the anterior stroma can also be imaged. Thiel Behnke dystrophy is characterized by hyperreflective material in a saw tooth configuration deposited on the surface of Bowman's layer often extending into the epithelium on AS-OCT. AS-OCT images of spheroidal degeneration show cystic structures in Bowman's layer and in the superficial corneal stroma. Granular dystrophy, which primarily affects the corneal stroma, is often found with hyperreflective material deposited in the anterior stroma with clear intervening spaces (Fig. 12a and b).

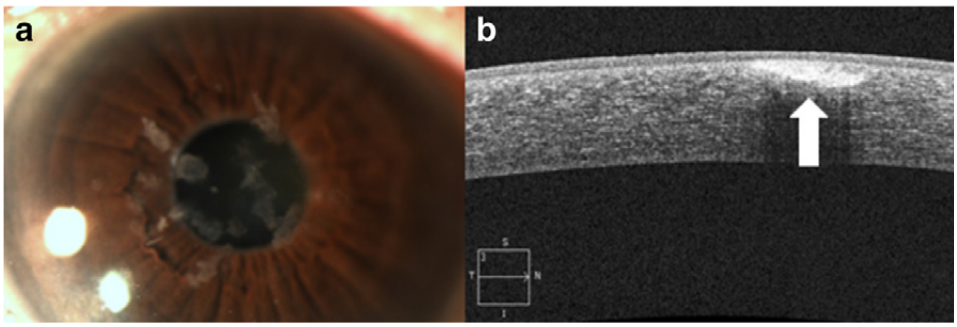

Fig. 12: Slit lamp photograph and AS-OCT of granular stromal dystrophy. **a** Slit lamp photograph of granular stromal dystrophy with positive Masson-Trichrome and negative amyloid staining. **b** On AS-OCT, there is hyperreflective material deposited in the anterior stroma with clear intervening spaces (*arrow*).

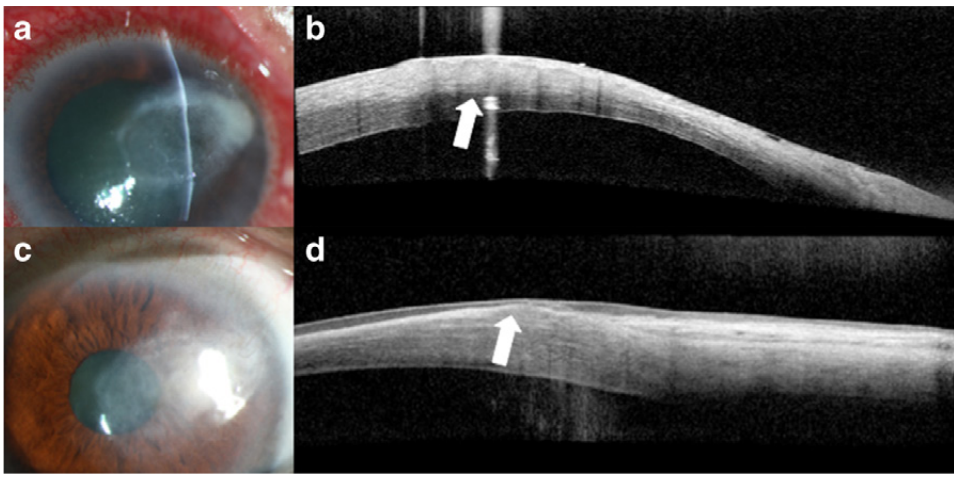

Fig. 13: Slit lamp photograph and AS-OCT of infectious keratitis and subsequent corneal scarring. **a** Slit lamp photograph of a patient with contact lens related *Pseudomonas* infectious keratitis. **b** AS-OCT shows diffuse stromal hyperreflectivity and thickening in the area of the infiltrate involving nearly 50% of the stroma (*arrow*). **c** Slit lamp photograph of a compact, subepithelial scar after infectious keratitis. **d** AS-OCT shows subepithelial thinning and hyperreflectivity in the area of the corneal scar (*arrow*).

Corneal infiltration in cases of microbial keratitis, which is often seen as hyperreflectivity in the corneal stroma with or without associated retrocorneal membrane formation may be visualized with AS-OCT (Fig. 13a and b). Serial AS-OCT images throughout the disease course can monitor corneal thickness, particularly areas of corneal thinning and scarring, which will appear as areas of subepithelial or stromal hyperreflectivity (Fig. 13c and d) [31]. Particularly in cases of *Acanthamoeba* keratitis, keratoneuritis can identified as highly reflective bands or lines in the anterior to mid stroma on AS-OCT. Sequential images can be used to establish the diagnosis and monitor for resolution [32].

Clinicians identify AS-OCT as useful in elucidating the depth of corneal opacities (i.e. corneal scarring or depositions) or lesions to assist surgeons in determining the optimal surgical procedure for visual rehabilitation [33]. Many times, the extent of corneal opacification can be evaluated by slit-lamp biomicroscopy alone, but AS-OCT can once again be valuable in certain cases where clinical examination proves challenging.

Epithelial debridement or superficial keratectomy can be employed for dystrophies or pathologies limited to the epithelium, subepithelium and/or Bowman's layer, while phototherapeutic keratectomy can be employed for pathologies limited to Bowman's layer and/or the anterior stroma. An anterior lamellar keratoplasty can be performed for pathologies extending into the anterior to mid stroma while a deep lamellar keratoplasty can be performed for pathologies extending into the posterior stroma. The AS-OCT can be most helpful in guiding the decision of which procedure to perform. When mostly anterior, femtosecond anterior lamellar keratoplasty is employed [34, 35]. Ultimately, a penetrating keratoplasty can be performed for full thickness or multi-layer corneal pathologies. Endothelial keratoplasty is reserved for pathologies affecting only the corneal endothelium. By understanding the precise location of the corneal pathology with the help of AS-OCT, the clinician can easily use the appropriate surgical intervention to ameliorate visual outcomes.

Use of AS-OCT for Anterior Segment Surgery

Anterior segment-optical coherence tomography has proven to be an effective tool to monitor the success and complications of several anterior segment surgical procedures including Descemet stripping automated endothelial keratoplasty (DSAEK), Descemet membrane endothelial keratoplasty (DMEK), laser-assisted in situ keratomileusis (LASIK) and even Boston Keratoprosthesis (Kpro) implantation [3].

Anterior segment-optical coherence tomography has also proven to be an excellent intraoperative adjunct for the anterior segment surgeon particularly during lamellar keratoplasty. Intraoperative OCT can be used to assess the effectiveness of Descemet's membrane stripping and determine the presence of subclinical interface fluid between the host cornea and DSAEK graft that could preclude complete graft attachment [36–38]. Post-operatively, high quality AS-OCT images can allow clinicians to assess graft adherence, graft centration, graft thickness and even epithelial remodeling after DSAEK surgery, all of which can affect the optical quality of corneas

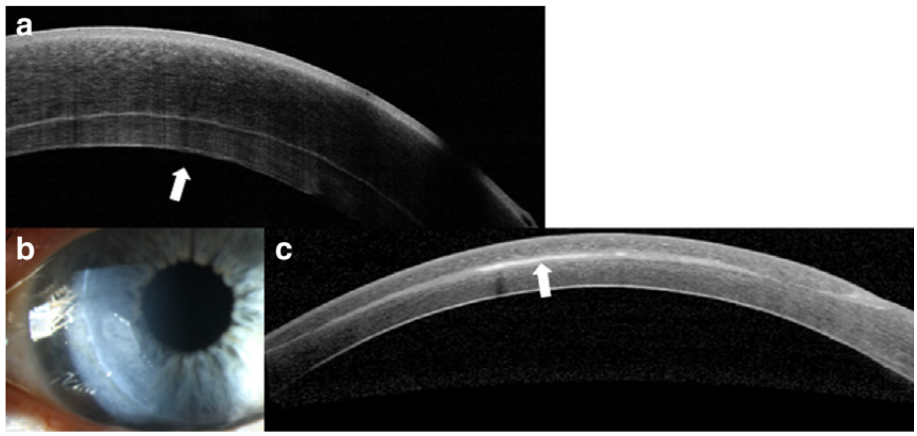

Fig. 14: Slit lamp photograph and AS-OCT of an attached DSAEK graft as well as epithelial ingrowth. **a** AS-OCT of an attached DSAEK graft (*arrow*) post-operatively. **b** Slit lamp photograph of epithelial ingrowth after LASIK. **c** AS-OCT demonstrating the area epithelial ingrowth after LASIK (*arrow*).

post-operatively [5, 39]. Swept-source OCT can even facilitate construction of 3-dimensional corneal topographic maps to quantitate post-operative corneal power, anterior and posterior corneal surface irregularity, intrastromal interface elevation, and pachymetry in post-DSAEK patients [40].

Clinicians can use AS-OCT imaging to help detect early graft detachments that may be challenging to diagnose with slit lamp biomicroscopy or Scheimpflug tomography, particularly in cases using very thin grafts (ultra-thin DSAEK or DMEK) or with persistent post-operative corneal edema or haze. Images evaluating the graft host interface can be obtained intra-operatively with the OCT machine mounted to the operating microscope [36] or post-operatively in the clinic (Fig. 14a). Moutsouris *et al.* [41] found that in patients with persistent stromal edema after DMEK, AS-OCT added a diagnostic value of 36% in helping discriminate early graft detachments from delayed corneal clearance and was found to be superior to corneal tomography and slit-lamp biomicroscopy in detecting early DMEK graft detachments. Swept-source OCT with protocols capturing limbus-to-limbus and irido-scleral views has also proven effective in detecting early graft detachments after DMEK, particularly when graft detachments were partial and poorly visible due to generalized corneal edema [42].

Implantation of the Type I Boston Kpro can often be associated with complications that can occur secondary to incomplete integration between the Kpro and surrounding cornea. Clinical examination of the Kpro-cornea interface can be difficult, but AS-OCT has shown to be a useful modality to image this interface and facilitate early detection of Kpro-associated complications. Our institution's ultra-high resolution AS-OCT has been used to capture images of the Kpro-cornea interface with two micron axial resolution [13]. AS-OCT images showed that the corneal epithelium covered the Kpro edge and sealed the potential space at the Kpro-cornea interface in 80% of cases. 20% of cases were found with a gap in the interface that was difficult to detect solely with slit-lamp examination. The authors posed that the lack of epithelial sealing around the Kpro edge might be associated with endophthalmitis. As such, more rapid and accurate identification of

incomplete integration of the Kpro-cornea interface with AS-OCT is of great utility and can help clinicians find methods to prevent infection sooner in at-risk patients [13].

Anterior segment-optical coherence tomography may be used to identify flap dislocations after laser-assisted in situ keratomileusis (LASIK). Images can also identify corneal structural changes associated with flap dislocation including macrostriae, flap edema, epithelial hyperplasia and epithelial ingrowth (Fig. 14b and c) associated with LASIK flaps [43].

Conclusion

With the introduction of high resolution AS-OCT for the ocular surface, cornea and anterior segment, we can ultimately aim to obtain "optical biopsies" of various ocular surface and anterior segment lesions in an era where we are moving towards more rapid and non-invasive diagnostic modalities. This innovative technology helps assess tissue anatomy and evaluate differences in cellular morphology and patterns to distinguish between divergent anterior segment conditions. While there is still room for growth with aspects of this imaging modality, its utility is already quite apparent and it is actively emerging as a promising clinical and research tool.

Abbreviations
AS-OCT: Anterior segment optical coherence tomography; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; Kpro: Keratoprosthesis; LASIK: Laser-assisted in situ keratomileusis; OSSN: Ocular surface squamous neoplasia

Funding
Ronald and Alicia Lepke Grant, The Lee and Claire Hager Grant, The Jimmy and Gaye Bryan Grant, The H. Scott Huizenga Grant, The Grant and Diana Stanton-Thornbrough, The Robert Baer Family Grant, The Emilyn Page and Mark Feldberg Grant, The Gordon Charitable Foundation, The Richard and Kathy Lesser Grant and The Richard Azar Family Grant (institutional grants).

Authors' contributions
All authors wrote, read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare they have no competing interests.

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Source: Venkateswaran, N., Galor, A., Wang, J. *et al*. *Eye and Vis* (2018) 5: 13. https://doi.org/10.1186/s40662-018-0107-0. © The Author(s). 2018.

Notes:

Dry Eyes Care Range

For Dry Eyes

℞ **Soha**

Sodium Hyaluronate 0.1% w/v sterile eye drops

In Mild to Moderate Dry Eyes

℞ **Eyemist**

(Hydroxypropyl Methylcellulose 0.3% + Stabilized Oxychloro Complex 0.005%)

In Chronic Dry Eyes, PRK and LASIK

℞ **Eyemist Forte**

HPMC 0.3 % + Dextran (70) 0.1 % + Glycerin 0.2 %

In Moderate to Severe Dry Eyes

℞ **Eyemist Gel**

Hydroxypropyl Methylcellulose (Hypromellose) Ophthalmic Gel 0.3%

In Moderate to Severe Dry Eyes

℞ **Cyclomune**

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