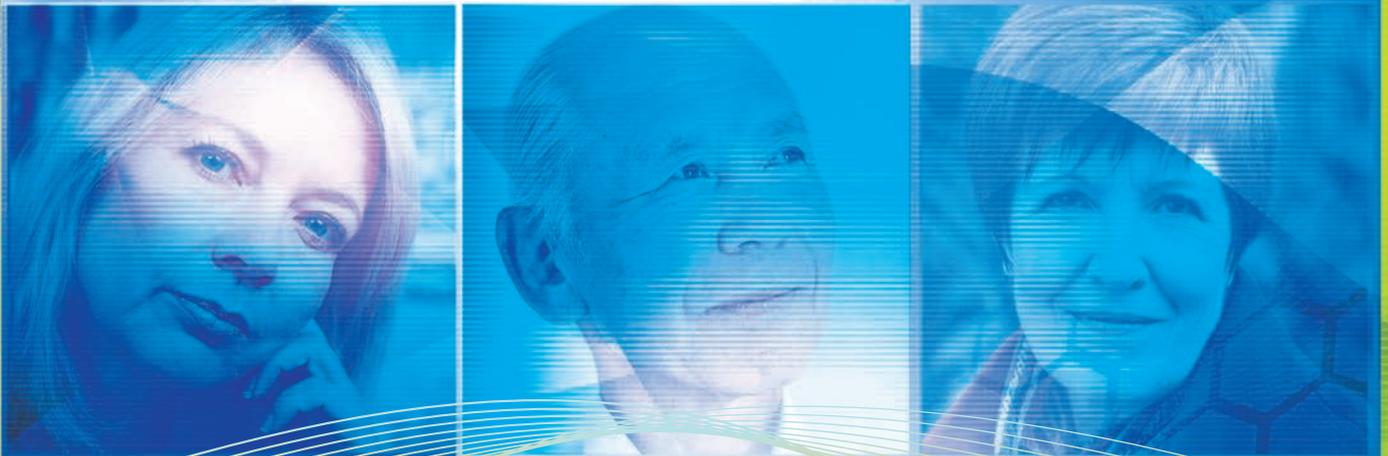


CME MONOGRAPH

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DRY EYE MANAGEMENT IN THE 21ST CENTURY

CHALLENGING CASE DISCUSSIONS



PROCEEDINGS FROM A CME SYMPOSIUM
HELD ON OCTOBER 17, 2016,
IN CHICAGO, ILLINOIS

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a CME symposium held on October 17, 2016, in Chicago, Illinois.

ACTIVITY DESCRIPTION

New tools are enabling better dry eye disease (DED) recognition and classification, and new options are available for DED management. This monograph provides an update on DED diagnosis and management through a series of short articles and case-based discussions.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists caring for patients with DED.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Discuss the prevalence of DED in various patient populations
- Evaluate and diagnose DED using at least 1 objective test, regardless of symptom severity
- Describe the implications of DED pathophysiology on diagnosis
- Incorporate evidence-based treatment and current guidelines for DED into practice

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DRY EYE MANAGEMENT IN THE 21ST CENTURY

CHALLENGING CASE DISCUSSIONS

INTRODUCTION

Dry eye disease (DED) is important to diagnose and treat. Newer point-of-care technologies and other tools are enabling DED recognition and classification. In addition, new options are available for DED management, and several novel therapies are in clinical trials. Understanding of the epidemiology of DED, its effect, and its pathophysiology provides a foundation for optimizing diagnosis and management. This activity highlights these topics through a series of short articles and case-based discussions.

PREVALENCE AND IMPACT OF DRY EYE DISEASE

EDWARD J. HOLLAND, MD

Dry eye disease is a very common ocular condition that has the potential to reduce quality of life, affect outcomes of ophthalmic surgery, and progress to cause permanent vision loss. Studies investigating the epidemiology of DED report prevalence rates ranging from 5.5% to 34%, depending on the population studied and the criteria used to identify DED.¹ In the United States, the Beaver Dam Study reported a DED prevalence of 14.4% among adults aged 48 to 91 years.² Data from the Beaver Dam Study and others show that the prevalence of DED is higher in women than in men and increases with age.²⁻⁴

A number of studies have also investigated the effect of DED on daily functioning and quality of life. Mild-to-moderate DED has been shown to interfere with usual activities, including work performance, willingness to drive at night, and performance of vision-intensive tasks.⁵ The effect of severe DED on quality of life has been ranked similar to that of severe angina or being on dialysis.^{6,7}

In addition, DED affects outcomes and patient satisfaction after cataract and refractive surgery, and these procedures can worsen DED because they affect corneal innervation [see **Sidebar: Diagnosis and Management of Dry Eye Disease Before Cataract Surgery**].⁸⁻¹⁰ The tear film, which is the first refractive interface of the eye, together with the cornea provides more than two-thirds of the eye's optical power.¹¹ An adequate and stable tear film is therefore necessary for good-quality vision, and is also necessary for accurate keratometric, topographic, and wavefront aberrometry measurements, which are used for planning corneal and IOL refractive correction (**Figure 1**).^{12,15}

Awareness of the prevalence of DED and its burdens underscores the importance for detection and effective treatment. Historically, however, DED has been underdiagnosed and undertreated.^{14,15}

Several reasons may explain these problems. Patients may self-treat, become asymptomatic because of neurotrophic changes

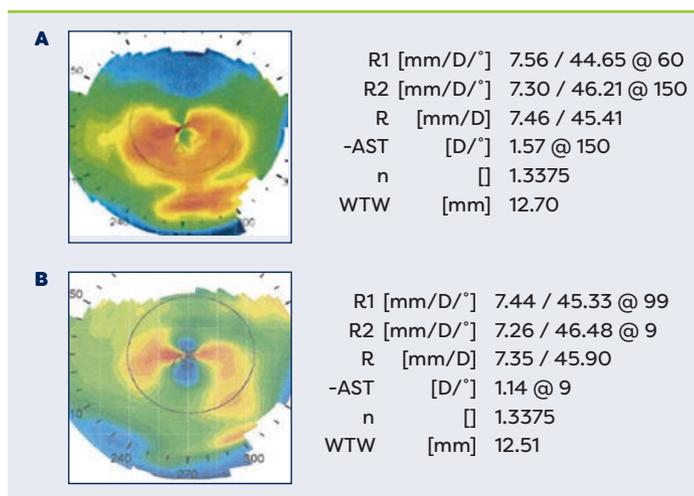


Figure 1. Topography and optical biometry findings (A) before and (B) after treating dry eye disease in a patient needing cataract surgery

Images courtesy of Preeya K. Gupta, MD

that develop with chronic disease, or fail to report their symptoms to their eye care provider. In a study of patients diagnosed by their ophthalmologist with blepharitis, approximately one-fourth had sought treatment for an unrelated reason and did not present with ocular surface-related symptoms as the chief complaint.¹⁶

Clinician behaviors may also be responsible for DED underdiagnosis and undertreatment. Because patients with DED may be regarded as demanding and hard to please, some clinicians may avoid initiating a diagnostic evaluation they expect will involve significant chair time and negatively affect practice efficiency. In addition, clinicians often think about DED only in terms of aqueous deficiency and therefore overlook meibomian gland dysfunction (MGD), which is the more common cause of DED.¹⁷ Newer diagnostic tests have improved the identification and classification of DED, but clinician implementation may be limited by uncertainty about

DIAGNOSIS AND MANAGEMENT OF DRY EYE DISEASE BEFORE CATARACT SURGERY

Dr Holland: An elderly patient with cataract and chronic dry eye disease (DED) may not complain about burning or stinging because of neurotrophic changes, but may have fluctuating vision because of DED. Fluctuating vision can persist after cataract surgery, causing the patient to be unhappy with the outcome of the surgery. What is your threshold for delaying cataract surgery because of DED, and how do you decide when it is okay to proceed after starting treatment?

Dr Milner: I am adamant about not operating on anyone with keratitis. I use fluorescein and lissamine green or rose bengal to look for keratitis. Fluorescein identifies the absence of epithelial cells, whereas lissamine green and rose bengal are vital dyes that identify damaged cells. I start treatment for DED if I see any staining, and I will not perform surgery until the keratitis is resolved or improved to its maximal level.

Dr Lane: In addition to resolution of staining, I look at the corneal topography for disappearance of irregularity in the mires and myriad colors on the map to decide if the patient is ready for surgery.

Dr Gupta: Corneal staining with fluorescein is a late finding, and almost everybody will have some staining after dilation. Therefore, I routinely use the matrix metalloproteinase-9 assay and tear osmolarity test to screen for DED. These 2 tests, along with querying about DED symptoms, can be easily done by a technician before I see the patient, so the screening does not affect practice efficiency.

Dr Holland: When I diagnose DED in a patient needing cataract surgery, I initiate treatment immediately and schedule the procedure for 6 to 8 weeks, but I tell the patient there is a chance the procedure will have to be delayed if significant findings of DED persist.

Dr Yeu: Some patients can become very frustrated if they are told they have to wait before scheduling their procedure. In my experience, mild-to-moderate ocular surface abnormalities can often improve within 3 to 6 weeks after starting topical corticosteroid treatment, and when there is more significant staining, the self-retaining amniotic membrane can be helpful to rapidly rehabilitate the ocular surface. With this in mind, I schedule surgery for 8 to 10 weeks out so that patients have a target date. Patients need to understand, however, that they have to be reexamined to be cleared for surgery, and they have to learn about the need for chronic treatment of DED postoperatively.

reimbursement. Some clinicians may also omit evaluation for DED because they believe there is no reason to diagnose a condition for which there is a lack of effective treatments.

The reality today, however, is that new diagnostic methods are often covered by insurance, can improve practice efficiency, and allow for more accurate diagnosis of DED. In addition, new treatments that allow for better outcomes and more satisfied patients, who can be a source of referrals, exist. For these reasons and, most importantly, because DED can be a progressive disease with significant adverse long-term sequelae, diagnosing and treating DED is the right thing to do.

UPDATES ON THE PATHOPHYSIOLOGY AND SUBTYPES OF DRY EYE DISEASE

MARK S. MILNER, MD, FACS

Understanding of the pathophysiology of DED has changed over the past few decades. Today, DED is recognized as a T cell-mediated inflammatory process involving the lacrimal glands and ocular surface tissues.^{18,19} It has been realized that DED is not just a problem of abnormal tear *quantity*, but that an abnormality of tear *quality* is also a cause. In addition, there is appreciation that DED is a chronic disease that may worsen if left untreated.

The normal tear film is composed of 3 major components: lipid, aqueous, and mucin.²⁰ The lipid component comes from meibomian gland secretions and prevents tears from evaporating too rapidly. The aqueous component is produced by the lacrimal gland and accessory lacrimal glands. The mucin component, which is produced by goblet cells, improves surface tension and increases viscosity. Tears also contain antimicrobial proteins, electrolytes for proper osmolarity, and growth factors, plus other chemical mediators that promote healing and suppress inflammation.

Chronic DED is associated with changes in all the tear film constituents. In addition to abnormalities in 1 or more of the 3 major components, the cytokine milieu changes to a proinflammatory state; there are alterations in electrolytes so that tears become hyperosmolar; tissue-damaging proteases become activated; and tear viscosity decreases.²¹⁻²³

Multiple factors can precipitate DED by causing irritation, inducing inflammation, or by directly affecting tissues that produce tear components, and these mechanisms can exacerbate DED by interacting with one another in a vicious cycle (**Figure 2**). Irritation leads to inflammation. The activated T cells release cytokines that cause tissue damage, thereby reducing tear production. The resultant unstable tear film produces the characteristic signs and symptoms of DED and increases irritation to perpetuate the pathophysiologic pathway.

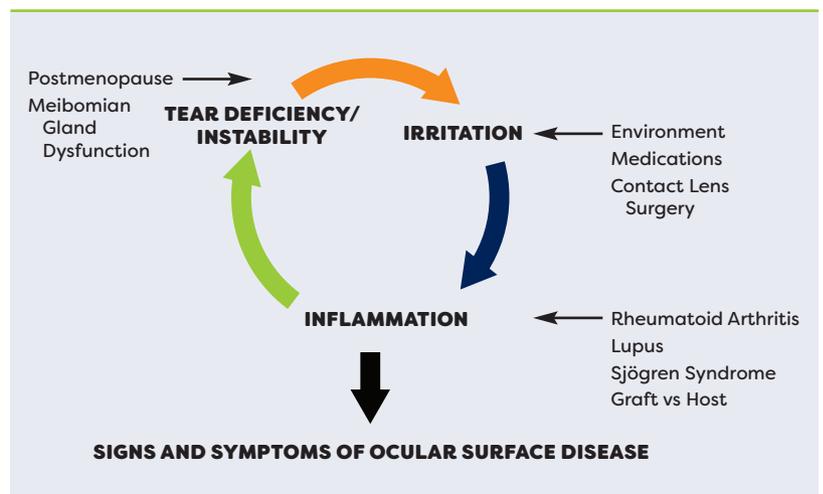


Figure 2. Dry eye disease triggers include multiple endogenous and exogenous factors

Desiccating stress causing tear film hyperosmolarity is considered the primary trigger for the cellular and molecular events in the immunoinflammatory pathway leading to DED (Figure 3).^{19,24} Increased tear osmolarity induces activation of T cells at the ocular surface, and cytokines released by the activated T cells activate antigen-presenting cells (APCs). The activated APCs migrate to the lymph nodes, where they cause upregulation of primed T cells. These T cells travel to the ocular surface through the circulation, and, after binding to antigens on the APCs, become activated to propagate the inflammatory response.

Dry eye disease is generally classified into 2 subtypes: aqueous deficient and evaporative.¹⁸ In aqueous-deficient DED, there is a lack of aqueous secretion by the lacrimal glands. In evaporative DED, lacrimal gland function is normal, but the tear film evaporates too quickly. Evaporative DED is more common than aqueous-deficient DED, although many patients have a mixed condition.¹⁷

Evaporative DED can be caused by poor lid function, a low blink rate, vitamin A deficiency, and contact lens wear, but MGD is the most common cause of evaporative DED and of DED overall.¹⁷ The pathophysiology of MGD involves a change in meibum composition and the effects of lid bacteria. In MGD, meibum transitions from unsaturated lipids that melt at body temperature to saturated fats that inspissate the meibomian glands. Bacteria on the lid margin secrete lipases that break the lipids down into soaps and free fatty acids. The soaps, which are seen as frothiness of the tear film at the lid margin, are irritants, and the free fatty acids are proinflammatory.

When evaluating patients with DED-like signs and symptoms, it is important to consider that a number of conditions can masquerade as or coexist with and exacerbate DED. Superior limbic keratoconjunctivitis, medicamentosa, superficial punctate keratitis of Thygeson, mucus fishing syndrome, contact lens-related toxicity, chemical toxicity, allergic/atopic conjunctivitis, conjunctivochalasis, and floppy lid syndrome, to name just a few, can all cause symptoms and/or signs that mimic or worsen those associated with DED. Maintaining an index of suspicion for these “co-conspirators,” in combination with a careful history and examination, is needed to make a correct diagnosis. The pattern of keratitis, as revealed by corneal staining, can provide helpful clues (Figure 4).²⁷ For example, keratitis in the interpalpebral fissure can be a sign of ultraviolet exposure, chemical toxicity, or mild DED. Diagnoses associated with inferior staining include blepharitis and lagophthalmos. Infranasal staining may raise suspicion of medicamentosa, and staining at 3 and 9 o'clock is classic for rigid gas permeable contact lens wear-related issues. Superior staining is suggestive of superior limbic keratoconjunctivitis, trachoma, or vernal keratoconjunctivitis. Accurate diagnosis allows for proper treatment.

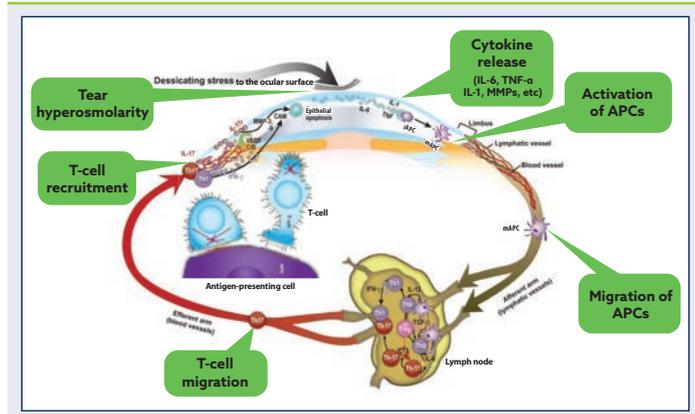


Figure 3. Dry eye immunoinflammatory pathway¹⁹

Abbreviations: APC, antigen-presenting cell; CAM, cell-adhesion molecule; IFN, interferon; IL, interleukin; iAPC, immature antigen-presenting cell; mAPC, mature antigen-presenting cell; MMP, matrix metalloproteinase; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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The binding between T cells and APCs is mediated by lymphocyte function-associated antigen-1 (LFA-1), which is expressed on the surface of T cells, and intercellular adhesion molecule 1 (ICAM-1), which is found on the surface of APCs.²⁵ ICAM-1 is also expressed on vascular endothelial cells and epithelial cells in inflamed tissues, where its interaction with LFA-1 mediates T-cell migration out of the vasculature and homing to the inflamed ocular surface.²⁵

Cyclosporine A and lifitegrast, the 2 anti-inflammatory treatments indicated specifically for the treatment of DED, act directly on the T cells but through different mechanisms. Cyclosporine A forms a complex with cyclophilin that inhibits the calcineurin phosphatase pathway, thereby inhibiting T-cell activation, production of inflammatory cytokines, and T-cell migration.²⁵ Lifitegrast is an LFA-1 antagonist that interferes with the LFA-1/ICAM-1 interaction.²⁶ Lifitegrast thereby prevents T-cell activation, cytokine release, and migration and the extravasation of new T cells into the inflamed ocular surface tissues.

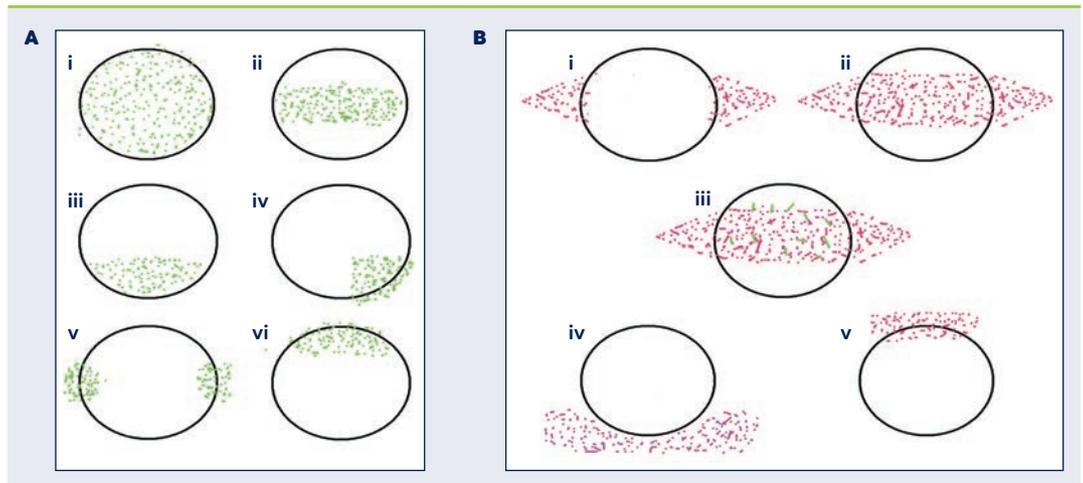


Figure 4. Staining patterns with (A) fluorescein and (B) rose bengal (or lissamine green) may help provide clues to the severity/etiology of dry eye disease or the diagnosis of a “co-conspirator.”²⁷ The fluorescein images are representative of (i) severe keratoconjunctivitis sicca, (ii) moderate keratoconjunctivitis sicca, (iii) blepharitis or exposure keratopathy, (iv) medication toxicity (right eye), (v) contact lens-related keratitis, and (vi) superior limbic keratoconjunctivitis or foreign body under lid, among others. The rose bengal images are representative of (i) mild, (ii) moderate, and (iii) severe presentations of keratoconjunctivitis sicca, among other diagnoses; filaments in an eye with severe keratitis sicca are depicted in green. Staining patterns associated with (iv) mucus fishing syndrome and (v) superior limbic keratoconjunctivitis or a foreign body under the lid are also shown.

Images courtesy of Mark S. Milner, MD, FACS

UPDATE ON NEW AND EMERGING THERAPEUTICS IN DRY EYE DISEASE

ELIZABETH YEU, MD

Previous algorithms for the management of DED were based on disease severity and involved treatments that were mainly palliative. Current strategies, enabled by an expanded therapeutic armamentarium, take into account the importance of targeting etiology and inflammation and include agents that may improve signs as well as symptoms.

EXISTING TREATMENTS

Ocular surface lubrication with artificial tears remains a cornerstone of DED treatment, and there is a growing variety of formulations to choose from in addition to the polymer-based products, such as those containing carboxymethylcellulose. Lipid emulsions that are more specific for evaporative DED have emerged. In addition, there are products containing hyaluronic acid that I believe cause less visual blur.

Accumulating data also support nutritional supplementation with essential fatty acids, which may provide benefit secondary to anti-inflammatory activity and by improving meibum composition.²⁸ In addition, vitamin A ointment can be very helpful, especially in patients who have keratinized lid margins.²⁹

For the management of MGD, application of warm compresses with digital lid massage has been the mainstay. The efficacy of this approach, however, tends to be limited because the compress generally does not stay sufficiently warm for the duration of application, and the posterior lid margin is less adequately heated through an anterior compression application. Also, patient compliance with this type of daily regimen can be poor. There are now a number of commercially available scrubs for lid cleansing, including tea tree oil-based products intended for treating *Demodex* mite infestation.³⁰ In addition, in-office treatments to clear obstructed meibomian glands have emerged. These approaches use motorized or mechanical devices, heat alone or with pulsation, intraductal probing, or intense pulsed light (IPL), which may be especially useful for patients with lid margin telangiectasias.³¹⁻³⁴

Medications used for DED treatment include a number of agents with anti-inflammatory activity. Topical cyclosporine A, 0.05%, has been available since 2003. In 2016, a multidose, preservative-free version, which features a proprietary dispensing tip design that maintains sterility of the bottle contents, was approved by the US Food and Drug Administration (FDA) (Figure 5).³⁵ Each bottle dispenses 60 doses, enough for 1 month of twice-daily use.



Figure 5. A multidose bottle of cyclosporine A, 0.05%, features a unidirectional valve and air filter technology that eliminates the need for a preservative

Image courtesy of Elizabeth Yeu, MD

Topical corticosteroids also have a role for short-term use in the management of DED. Oral doxycycline, oral azithromycin, and topical azithromycin can be part of a DED treatment strategy and offer anti-inflammatory properties in addition to other mechanisms of action.³⁶

Topical lifitegrast, 5%, was approved in July 2016 for the treatment of the signs and symptoms of DED.³⁷ Its efficacy and safety were demonstrated in four 12-week, placebo-controlled studies, including 1 phase 2 study and 3 phase 3 studies known as OPUS-1, OPUS-2, and OPUS-3, respectively.³⁸⁻⁴¹

In OPUS-1, lifitegrast met its sign coprimary end point, achieving statistically significant superiority to placebo for reducing inferior corneal staining ($P = .0007$).³⁹ Although lifitegrast did not meet the symptom coprimary end point of visual-related ocular surface disease index (OSDI) function subscale score, a benefit for symptom improvement in the eye dryness score was observed in a post hoc analysis, particularly in patients who seemed more symptomatic at baseline.^{25,39} Such patients were targeted for enrollment in OPUS-2 and OPUS-3. In a primary end point analysis in both studies, lifitegrast demonstrated statistically significant superiority to placebo for improving the eye dryness score at day 84 ($P \leq .0007$) (Figure 6).^{40,41} In addition, it provided significant symptom relief by day 14.^{40,41}

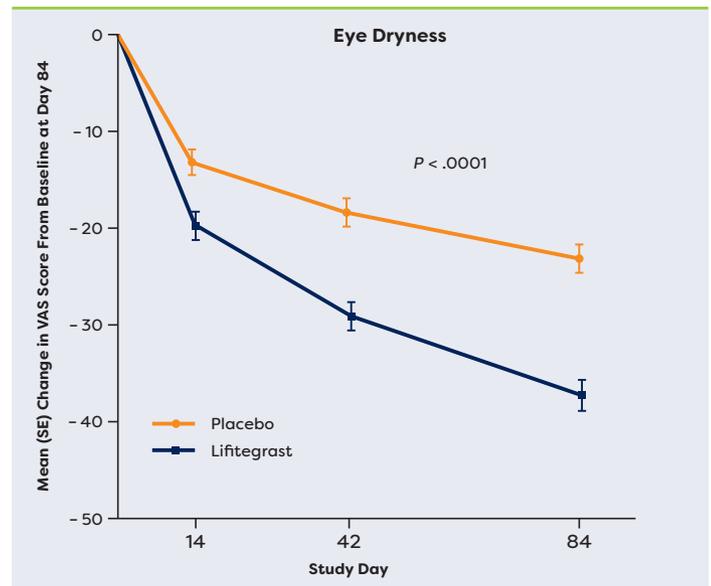


Figure 6. Change from baseline to day 84 eye dryness score (coprimary end point) in the placebo and lifitegrast groups in OPUS-2⁴⁰

Abbreviations: SE, standard error; VAS, visual analogue scale.

Lifitegrast was well tolerated in premarketing clinical trials.³⁹⁻⁴¹ The most common treatment-emergent adverse events were instillation site irritation, dysgeusia, and reduced visual acuity, all of which tend to disappear with ongoing use.

INVESTIGATIONAL THERAPIES

Emerging treatments for DED include a new essential fatty acid-based artificial tear, along with a perfluorohexyloctane-based artificial tear for the treatment of evaporative DED. In addition, cyclosporine formulated in the perfluorohexyloctane vehicle is in clinical trials,⁴² as are some novel corticosteroid products, including an absorbable, dexamethasone-releasing intracanalicular depot and a formulation of loteprednol that improves mucus penetration.^{43,44}

In July 2016, an application was filed with the FDA for approval of an intranasal tear neurostimulator.⁴⁵ The device uses disposable tips and stimulates a reflex pathway that induces production of aqueous, mucin, and lipids.⁴⁶

Tavilermide, 1%, ophthalmic solution is also in late-phase clinical development.⁴⁷ Tavilermide is a neurotrophin mimetic that acts as a partial agonist of the nerve growth factor receptor TrkA.⁴⁸ Nerve

growth factor binding to TrkA supports corneal nerve function and epithelial health and stimulates mucin secretion.^{48,49}

In addition, recruitment is under way for a phase 3 study investigating topical RGN-259 for the treatment of DED.⁵⁰ RGN-259 is an antagonist of thymosin beta-4, a peptide naturally found in various human blood cells that has anti-inflammatory activity and promotes tissue repair.⁵¹ RGN-259 demonstrated a rapid onset of action in a phase 2 clinical trial and is being developed in a preservative-free formulation.⁵¹

Other novel topical treatments being developed for DED include SkQ1 and cis-urocanic acid. SkQ1 is a small molecule that acts within the mitochondria as a reactive oxygen species scavenger, reducing mitochondrial oxidative stress.⁵² After oxidation in the mitochondria, SkQ1 is reduced by the respiratory chain and regenerates itself, which suggests the potential for infrequent dosing. Cis-urocanic acid is a natural component in human skin that has anti-inflammatory activity.⁴⁸

CASE 1: PATIENT WITH SJÖGREN SYNDROME

FROM THE FILES OF PREEYA K. GUPTA, MD

A 45-year-old woman is referred because of chronic eye irritation, burning, and photophobia. She has been using preservative-free artificial tears very frequently, up to 10 times a day, and an artificial tear ointment at bedtime. She has a family history of rheumatoid arthritis and no remarkable personal medical history. On the review of systems, she reports dry mouth and periodic joint pains.

Clinical examination shows 1-2+ corneal punctate epithelial erosions and 2+ conjunctival punctate epithelial erosions OU. Tear break-up time (TBUT) is 7 to 8 s, matrix metalloproteinase-9 (MMP-9) is positive OU, and tear osmolarity is 318/330 mOsm/L OD/OS.

Dr Gupta: What do you include in your examination to screen for DED?

Dr Holland: We empower the technicians to discuss DED symptoms with the patients and use a questionnaire to help with screening. Patients with DED-related symptoms have point-of-service testing that includes tear osmolarity. Elevated tear osmolarity is a sign of DED, but does not help to determine the type, so we recently added meibography. I am glad to have the meibomian gland images in hand when I see the patient and that the technician will have already discussed MGD with the patient.

Dr Gupta: I feel point-of-care testing has revolutionized how I practice in terms of treating and diagnosing DED. With these tests, I am finding DED earlier and more often than before, which has been especially valuable for patients who are coming in for cataract or refractive surgery.

The tear osmolarity test is CLIA-waived and can be easily done by technicians. The result is generated within seconds, and a reading above 308 mOsm/L or an intereye difference > 10 mOsm/L raises suspicion for DED.⁵³ Variability in osmolarity readings between visits is also highly suggestive of DED.⁵⁴

MMP-9 is another point-of-care test for DED that is also CLIA-waived.⁵⁵ MMP-9 is an inflammatory marker, and a positive result, indicated by the development of a red line, occurs when the MMP-9 concentration in the tear sample is ≥ 40 ng/mL.⁵⁶ The test has been shown to have high sensitivity and specificity for diagnosing DED.⁵⁷ Elevated MMP-9, however, is a nonspecific marker of inflammation, and the test result is not quantitative, although darkness of the red line may provide a qualitative indication of the level of MMP-9 (**Figure 7**).

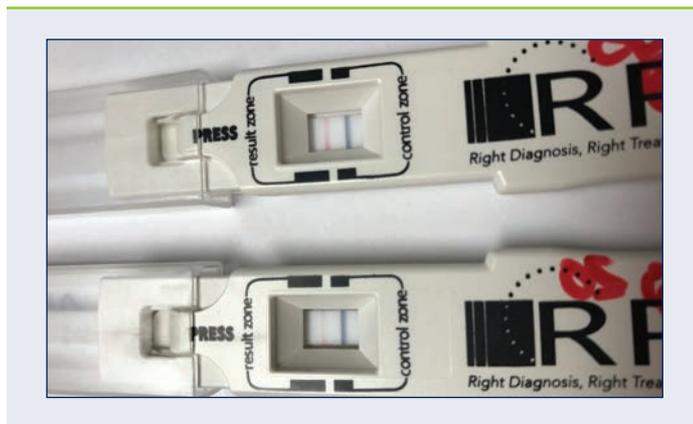


Figure 7. Results from the matrix metalloproteinase-9 (MMP-9) assay. The presence of both a red and blue line in the windows of the top and bottom devices indicates a positive result (MMP-9 ≥ 40 ng/mL). On the basis of the greater intensity of the red line, the concentration of MMP-9 is assumed to be higher in the tear sample obtained with the top device.

Image courtesy of Preeya K. Gupta, MD

Dr Holland mentioned the use of questionnaires. There are several structured tools that are easy to implement for DED screening, all of which are available for free online, including the OSDI, Standard Patient Evaluation of Eye Dryness, and Symptom Assessment in Dry Eye. A basic clinical examination is also important for DED diagnosis. Does anyone use the Schirmer test?

Dr Holland: I do not do a Schirmer test routinely. I think it has value only when the result is 0 mm. I would use it in a patient like this, who I suspect has Sjögren syndrome.

Dr Milner: I do not want there to be anesthetic in the eye before I see the patient because the anesthetic will decrease the blink reflex and contains a preservative, both of which can lead to artifactual punctate staining. I therefore prefer to do the Schirmer test without anesthetic. A result of < 10 mm after 5 minutes is considered diagnostic of DED. When the test is done without anesthesia, a Schirmer score < 10 mm is highly indicative of aqueous deficiency because the conjunctiva is being stimulated without anesthetic and the patient still cannot mount a reflex tear response. I consider such a patient to be a candidate for punctal plugs. If a patient has signs and symptoms of DED with a Schirmer test result of 30 mm, I look for other causes of DED, such as MGD, using meibography, lipid layer interferometry, and lid margin assessment.

I also use rose bengal or lissamine green for staining in every patient because the findings with the vital dyes help me make an accurate diagnosis, look for DED co-conspirators, and select appropriate treatment (**Figure 4**). Although I think it is forgotten by many clinicians, I believe it is also critical to measure TBUT routinely. A rapid TBUT is usually associated with evaporative DED, which is most commonly caused by MGD. Mucin deficiency associated with goblet cell loss, however, is often missed as the cause of an unstable tear film characterized by a rapid TBUT. Goblet cell loss is present in patients with conjunctival scarring, which occurs with ocular cicatricial pemphigoid, Stevens-Johnson syndrome, and chemical injury, and the standards for identifying goblet cell deficiency are impression cytology or conjunctival biopsy. These techniques, however, are not clinically practical. If I see a patient with a rapid TBUT who does not have MGD and/or who has conjunctival scarring, I assume there is goblet cell deficiency. Topical vitamin A has been shown to replenish goblet cells.⁵⁸ I and others have used compounded vitamin A ointment to treat patients with goblet cell deficiency.²⁷

In a patient with DED and dry mouth, I would also do the newer point-of-care Sjögren test that assays 4 traditional biomarkers—Sjögren-specific antibody A, Sjögren-specific antibody B, antinuclear antibody, and rheumatoid factor—along with 3 novel proprietary biomarkers—salivary protein-1, carbonic anhydrase VI, and parotid secretory protein.⁵⁹ I have had patients who tested negative with the traditional laboratory screening for Sjögren syndrome test positive with the newer test.

Dr Gupta: A blood specimen for the newer test can be obtained in the office and sent out for analysis. The blood can be from a fingerstick that is applied to a test card or drawn into a vial.⁶⁰ With its additional markers, the newer test may increase the potential for earlier diagnosis, although more data are needed to evaluate its performance. Regardless, it is important to diagnose Sjögren syndrome as early as possible because it can be associated with systemic conditions, including lymphoma, lupus, systemic sclerosis, and other autoimmune disorders.⁶⁰ Returning to the patient, she is already using artificial lubricants. What treatment would you add?

Dr Lane: I have always been an advocate for a short-term course of a topical corticosteroid in a patient with severe symptoms because it can be effective to put the fire out, so to speak, and a topical corticosteroid is also helpful as induction therapy when starting topical cyclosporine.⁶¹ Now that lifitegrast is available, I would initiate its use instead of cyclosporine because lifitegrast has a rapid onset of action, and I believe it is more comfortable for the patient on instillation during early use. I would start lifitegrast together with or shortly after starting a topical corticosteroid, such as loteprednol etabonate gel. My choice of loteprednol considers its lower potential to cause IOP elevation and cataract formation compared with other topical corticosteroids.⁶² I would not argue, however, with anyone who would use lifitegrast alone without a corticosteroid, which may in fact be unnecessary.

Dr Holland: I think that lifitegrast by itself might be sufficient for most patients with aqueous-deficient DED. For a patient like this, in which there is suspicion of Sjögren syndrome, however, I would be worried about progressive inflammation of the lacrimal glands and conjunctiva. For this reason, I would start her on loteprednol with lifitegrast.

Dr Gupta: Both lifitegrast and cyclosporine could be considered for inflammation control in this patient, but I chose lifitegrast because of its rapid onset of action for improving symptoms. Her MMP-9 test turned from positive to negative, and tear osmolarity improved to normal range values. I was a little surprised to see that her TBUT also improved, although topical cyclosporine has been shown in a randomized controlled trial to improve tear film stability in patients with MGD.⁶³ I am often asked if anti-inflammatory medications are helpful for MGD-related DED, considering that the pivotal trials investigating them enrolled patients with aqueous-deficient DED. An understanding of the pathophysiology of DED, however, makes it clear that MGD can lead to inflammation of the ocular surface by causing tear film instability. Therefore, it seems logical that anti-inflammatory therapies can be useful. I also send patients with Sjögren syndrome to a rheumatologist because they need evaluation for and management of any extraocular disease.

Dr Holland: Dry eye disease associated with Sjögren syndrome is a severe condition, and I think it often needs to be managed with systemic therapy. This is another reason why I like to partner with a rheumatologist to provide care. Even if the patient has no evidence of systemic disease, I will suggest systemic immunosuppression for progressive DED.

CASE 2: PATIENT WITH MEIBOMIAN GLAND DYSFUNCTION

FROM THE FILES OF STEPHEN S. LANE, MD

A 66-year-old man reports having irritated red eyes for several years, along with crustiness upon waking up in the morning, fluctuating vision, and intermittent poor vision. His family physician prescribed topical erythromycin ointment to be applied to the lids. He has been on topical cyclosporine for a short time.

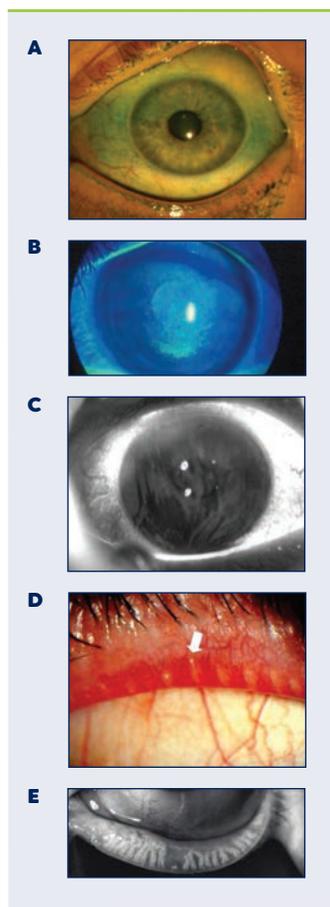


Figure 8. Images from (A-D) slit-lamp examination and (E) meibography in a patient with meibomian gland dysfunction

Images courtesy of Stephen S. Lane, MD

Clinical examination shows interpalpebral conjunctival staining with lissamine green (Figure 8A), punctate epithelial changes of the central cornea with fluorescein (Figure 8B), and an irregular, streaky-appearing tear film with fluorescein staining (Figure 8C). There is inspissation of the meibomian glands (Figure 8D), and lid expression releases opaque, white, thickened meibum from the meibomian glands. Tear osmolarity is 297/312 mOsm/L OD/OS, and the MMP-9 test is negative. Tear film lipid layer interferometry shows abnormal thickness, especially in the right eye, and meibomian gland atrophy and attenuation is seen on meibography (Figure 8E).

Dr Lane: This patient clearly has MGD. I think meibography has tremendous value for patient education. When patients are shown their images and images from an eye without MGD, they can easily appreciate that they have a problem and understand what MGD is. For these reasons, patients tend to be amenable to and compliant with whatever treatment I recommend.

Dr Milner: On the basis of the interpalpebral fissure staining with lissamine green, I think this patient also has aqueous-deficient DED. I would confirm this with a Schirmer test and then treat according to the diagnosis of a mixed type of DED.

Dr Holland: I agree that with MGD, staining is typically seen in the inferior cornea. However, I do not think a Schirmer test is needed to diagnose aqueous-deficient DED. The test is problematic because it results in many false negatives.

Dr Lane: There is no question that this patient may have a mixed type of DED, but I think MGD is the most prominent problem. When I encounter such a situation, I would treat the MGD first. I would initiate treatment for aqueous-deficient DED later if signs and symptoms consistent with aqueous-deficient DED persist after the MGD is controlled. How do you tell if *Demodex* infestation is present in a patient with lid margin disease?

Dr Gupta: There are a couple of ways to identify *Demodex*. I epilate an eyelash and look for mites under magnification using an inexpensive microscope I keep in the clinic. Alternatively, with the patient at the slit lamp and while pulling on an eyelash, I look for cylindrical dandruff encircling the eyelash base. An inflamed, red, irritated appearance of the lid margins is also a clue.

Dr Lane: Initial treatment for MGD could include oral omega-3 fatty acids, lid scrubs, and lipid-based artificial tears. These modalities could be started simultaneously or sequentially as needed. I think oral omega-3 fatty acids are very important for a patient with MGD. Lid scrubs can be beneficial, but patient compliance is poor.

This patient was started on all 3 therapies. When he returned 1 month later, he admitted to stopping the lid scrubs. His symptoms have slightly improved, but his tear osmolarity, lipid layer interferometry, and meibography are unchanged.

Other treatments to consider for MGD include oral doxycycline, topical or oral azithromycin, and in-office lid treatments. I would particularly consider oral doxycycline in a patient with rosacea, and making that diagnosis necessitates examination of the facial skin, especially in the nasal area. What treatment would you now recommend for this patient?

Dr Yeu: It depends on how symptomatic he is and the severity of the lid margin disease. The MGD in this patient seems to be moderately severe, and it appears that he has up to 20% loss of his meibomian glands. I would recommend an in-office lid treatment because I think it will be helpful to maintain his existing glands. I would also encourage thermal pulsation therapy. I prescribe a short course of a topical corticosteroid to patients who have that procedure because it can be irritating, and I would couple it with at-home lid hygiene. Topical azithromycin can be helpful, but I find oral azithromycin given in a pulse regimen is especially useful for patients with more severe disease, especially those who do not seem to be doing well with oral doxycycline. I prescribe azithromycin 250 or 500 mg once a day for 3 consecutive days of the week over 6 to 8 weeks.

Dr Lane: Azithromycin has anti-inflammatory and antibacterial activity, and it has been shown to alter the meibum composition and improve signs and symptoms in patients with MGD.³⁶

Dr Gupta: I offer IPL and thermal pulsation to patients with MGD. Intense pulsed light is performed once a month for 4 sessions. The light is applied underneath the lower lid across the cheeks and nose, and this is followed by manual gland expression. Thermal pulsation is a more comfortable procedure and done in a single session. In my experience, more patients choose thermal pulsation over IPL, but I especially recommend IPL to patients with more severe meibomian gland atrophy because I think they benefit from the repeated gland expression. I also recommend IPL with a broader facial application to patients with rosacea.

Dr Lane: This patient was treated with thermal pulsation. The unit delivers heat to the meibomian gland side of the interpalpebral area of the lid and provides simultaneous pulsation, which opens the obstructed glands. Treatment takes approximately 12 minutes, and both eyes are done at the same time.

In a randomized controlled trial of thermal pulsation conducted for FDA approval, there was progressive improvement in the mean meibomian gland score and mean OSDI score at follow-up visits at 2 and 4 weeks posttreatment (**Figure 9**).³² The study had a crossover design, and the untreated control group also showed a treatment benefit at 2 weeks after a thermal pulsation procedure. Other studies have corroborated these findings and reported that after a single treatment, significant improvements were still present at 1 and 3 years.^{64,65}

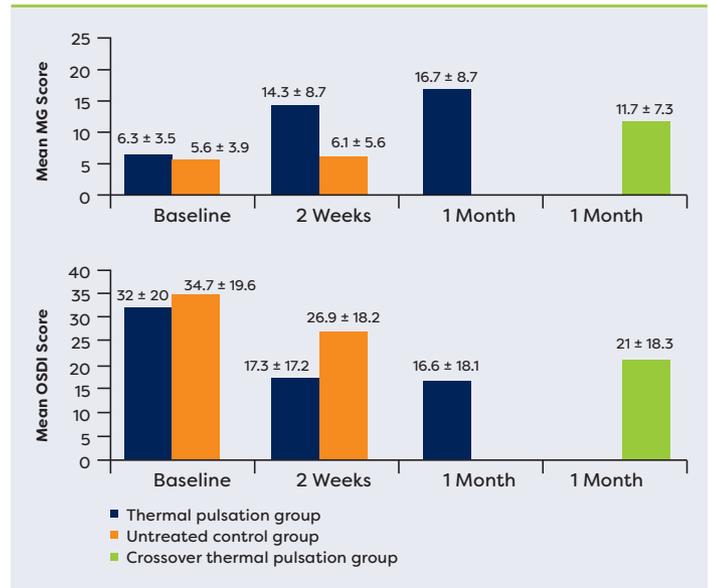


Figure 9. The thermal pulsation procedure demonstrated significant benefits for improving the meibomian gland (MG) score and Ocular Surface Disease Index (OSDI) score compared with placebo in a US Food and Drug Administration clinical trial³²

The patient in the case returned 1 month after receiving thermal pulsation treatment and reported significant symptom improvement. He also had improvement in the appearance of the meibomian glands, tear osmolarity, and lipid layer thickness.

TAKE-HOME POINTS

Dry eye disease is a common, progressive, T cell-mediated inflammatory disease affecting vision, comfort, quality of life, and outcomes of ophthalmic surgery.

New diagnostic technologies and treatments are now available, so that clinicians can no longer ignore DED, but must take a proactive approach to detect this disease.

Diagnosis and management of DED should consider that 2 subtypes (aqueous deficient and evaporative) often coexist, and the presence of other disorders can mimic or exacerbate DED.

Multiple factors can trigger DED by causing irritation and inflammation or affecting tear film quality and/or quantity.

Lifitegrast is a new topical, anti-inflammatory agent approved for treating the signs and symptoms of DED.

The DED product pipeline features many promising therapies, including novel formulations of current modalities and first-in-class medications.

Dry eye disease and its related inflammation should be treated before proceeding with cataract or corneal surgery.

Sjögren syndrome causes very severe DED and has multiple systemic complications. Early diagnosis and referral to a rheumatologist are important.

Meibomian gland dysfunction is the most common cause of DED, and newer in-office treatments for treating meibomian gland obstruction are improving its management.

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FOR INSTANT PROCESSING, COMPLETE THE CME POST TEST ONLINE

[HTTPS://TINYURL.COM/DRYEYE21STCENTURY](https://tinyurl.com/dryeye21stcentury)

CME POST TEST QUESTIONS

To obtain *AMA PRA Category 1 Credit™* for this activity, complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/Credit Request form on the following page. Alternatively, you can complete the CME Post Test online at <https://tinyurl.com/DryEye21stcentury>.

See detailed instructions at **To Obtain AMA PRA Category 1 Credit™ on page 2.**

- Epidemiologic studies report the prevalence of DED ranges from approximately:
 - 5% to 34%
 - 15% to 34%
 - 25% to 50%
 - 34% to 65%
- The most common cause of DED is:
 - Age-related lacrimal gland obstruction
 - Decreased estrogen in postmenopausal women
 - Meibomian gland dysfunction
 - Sjögren syndrome
- Dessicating stress initiates the pathogenic pathway leading to DED by:
 - Activating phospholipase 2, resulting in prostaglandin synthesis
 - Causing tear film hyperosmolarity
 - Increasing exposure of antigens on ocular surface cells
 - Upregulating MMP-9
- What tear osmolarity result is suggestive of dry eye?
 - Intereye difference > 5 mOsm/L
 - Value > 290 mOsm/L
 - Value > 305 mOsm/L
 - Variability in readings between visits
- In a patient with DED, which of the following is evidence of inflammation?
 - Low TBUT
 - Low tear osmolarity
 - Positive MMP-9 test
 - Superior corneal staining
- Findings of dry eye, cylindrical dandruff encircling the eyelash base, and lid margin erythema should raise suspicion for:
 - Demodex* infestation
 - Medicamentosa
 - Ocular rosacea
 - Staphylococcal blepharitis
- Which of the following is not an in-office approach for relieving meibomian gland obstruction?
 - IPL treatment
 - Intraductal probing
 - Radiofrequency microneedling with manual gland expression
 - Warming with mechanical pulsation
- In the phase 3 OPUS-2 clinical trial, how early did lifitegrast, 5.0%, demonstrate a statistically significant response vs placebo for improving the symptom of eye dryness?
 - 7 days
 - 14 days
 - 1 month
 - 3 months
- A patient presents with complaints of mild ocular discomfort and itching. An evaluation for DED shows limited corneal staining, mildly altered meibum on lid expression, no meibomian gland dropout on meibography, negative MMP-9, and tear osmolarity 314 mOsm/L OD, 312 mOsm/L OS. Which treatment regimen might be considered appropriate for this patient?
 - Lid hygiene, artificial tears, and IPL treatment
 - Lid hygiene, artificial tears, and oral omega-3 fatty acid supplementation
 - Lid hygiene, artificial tears, and topical lifitegrast
 - Lid hygiene, topical corticosteroid (2 weeks), and topical cyclosporine
- A patient with DED, with elevated tear film osmolarity and a positive MMP-9 test, is eager to have cataract surgery performed as soon as possible. To try to meet this desire, which treatment strategy might be considered the most appropriate for this patient?
 - Artificial tear ointment with oral doxycycline 200 mg twice daily
 - Preservative-free artificial tears with punctal occlusion
 - Topical cyclosporine A with artificial tears
 - Topical corticosteroid with artificial tears

ACTIVITY EVALUATION/CREDIT REQUEST

Original Release: May 1, 2017

Last Review: April 3, 2017

Expiration: May 31, 2018

Dry Eye Management in the 21st Century: Challenging Case Discussions

To receive *AMA PRA Category 1 Credit™*, you must complete this **Evaluation** form and the **Post Test**. Record your answers to the **Post Test** in the **Answer Box** located below. Mail or Fax this completed page to **New York Eye and Ear Infirmary of Mount Sinai–ICME**, 485 Madison Avenue, 17th Floor, New York, NY 10022 (Fax: 212-353-5703). Your comments help us to determine the extent to which this educational activity has met its stated objectives, assess future educational needs, and create timely and pertinent future activities. Please provide all the requested information below. This ensures that your certificate is filled out correctly and is mailed to the proper address. It also enables us to contact you about future CME activities. Please print clearly or type. Illegible submissions cannot be processed.

PARTICIPANT INFORMATION (Please Print) Home Office

Last Name _____ First Name _____

Specialty _____ Degree MD DO OD PharmD RPh NP RN PA Other _____

Institution _____

Street Address _____

City _____ State _____ ZIP Code _____ Country _____

E-mail _____ Phone _____ Fax _____

Please note: We do not sell or share e-mail addresses. They are used strictly for conducting post-activity follow-up surveys to assess the impact of this educational activity on your practice.

Learner Disclosure: To ensure compliance with the US Centers for Medicare and Medicaid Services regarding gifts to physicians, **New York Eye and Ear Infirmary of Mount Sinai** Institute for CME requires that you disclose whether or not you have any financial, referral, and/or other relationship with our institution. **CME certificates cannot be awarded unless you answer this question.** For additional information, please call NYEE ICME at 212-979-4383. Thank you.

Yes No I and/or my family member have a financial relationship with **New York Eye and Ear Infirmary of Mount Sinai** and/or refer Medicare/Medicaid patients to it.

I certify that I have participated in the entire activity and claim **1.5 AMA PRA Category 1 Credits™**.

Signature Required _____ Date Completed _____

OUTCOMES MEASUREMENT

Yes No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answered "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:

5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

• Discuss the prevalence of DED in various patient populations	5	4	3	2	1
• Evaluate and diagnose DED using at least 1 objective test, regardless of symptom severity	5	4	3	2	1
• Describe the implications of DED pathophysiology on diagnosis	5	4	3	2	1
• Incorporate evidence-based treatment and current guidelines for DED into practice	5	4	3	2	1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know. _____

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?

4 = definitely will implement changes 3 = likely will implement changes 2 = likely will not implement any changes 1 = definitely will not make any changes

4 3 2 1

Please describe the change(s) you plan to make: _____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face? _____

4. Number of patients I see per week with dry eye 1–10 11–20 21–40 41–60 more than 60

5. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity. Patient Care Practice-Based Learning and Improvement Professionalism

Medical Knowledge Interpersonal and Communication Skills Systems-Based Practice

6. What other topics would you like to see covered in future CME programs? _____

ADDITIONAL COMMENTS _____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9	10