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INDIVIDUALIZED MANAGEMENT OF PATIENTS WITH DRY EYE DISEASE

PART 1

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Individualized Management of Patients With Dry Eye Disease

Part 1

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion.

ACTIVITY DESCRIPTION

This activity focuses on providing ongoing and continuous education with up-to-date information and cases for anterior segment specialists, and general ophthalmologists involved in the treatment and management of patients with dry eye disease.

TARGET AUDIENCE

This certified CME activity is designed for anterior segment specialists, general ophthalmologists, and other eyecare practitioners involved in the management of dry eye disease.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Discuss** the mechanism of action of dry eye disease.
- **Evaluate** the signs and symptoms in patients with dry eye complaints.
- **Discuss** the prevalence of dry eye disease.
- **Develop** a differential diagnosis for patients with complaints of dry eye.

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1. PLEASE RATE YOUR CURRENT CONFIDENCE ON YOUR ABILITY TO APPLY UPDATES IN THE MANAGEMENT OF DRY EYE DISEASE IN THE CLINIC. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT.)

a. 1
b. 2
c. 3
d. 4
e. 5

2. PLEASE RATE HOW OFTEN YOU APPLY ADVANCED DRY EYE DISEASE MANAGEMENT IN THE CLINIC. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS.)

a. 1
b. 2
c. 3
d. 4
e. 5

3. THE 2017 TEAR FILM AND OCULAR SURFACE DRY EYE WORKSHOP II REVISED THE DEFINITION OF DRY EYE DISEASE IN ALL THE FOLLOWING WAYS EXCEPT:

a. It created a new classification scheme of dry eye disease.
b. It excluded neurosensory abnormalities from the definition of dry eye disease.
c. It recognizes the multifactorial nature of dry eye as a disease where loss of homeostasis of the tear film is the central pathophysiological concept.
d. It removed visual impairment and the impact the disease has on visual function from the definition.

4. THE FOLLOWING ARE SYMPTOMS OF DRY EYE DISEASE EXCEPT:

a. Itching, burning eyes
b. A gritty, foreign-body sensation in the eyes
c. Glare, starbursts, or halos
d. Neuropathic pain

5. IDENTIFY THE POPULATION OF PATIENTS IN WHICH DRY EYE DISEASE IS BECOMING MORE PREVALENT.

a. People aged 18 to 34
b. Postmenopausal women over age 50
c. Women aged 34 to 50 with autoimmune diseases
d. Men aged 35 to 50 who have had refractive surgery

6. THE PREFERRED DIAGNOSTIC TEST FOR CONFIRMING DRY EYE DISEASE IS _____

a. Schirmer test
b. Lissamine green
c. Tear osmolarity
d. Fluorescein

7. THE _____ IS CONSIDERED USEFUL TECHNOLOGY IN THE CLINIC FOR HISTOLOGIC EXAMINATION OF THE OCULAR SURFACE.

a. LipiView
b. TearLab Osmolarity System
c. Confocal microscope
d. Keratograph

8. ACCORDING TO THE PANELISTS, WHAT SHOULD BE THE IDEAL BIOMARKER FOR DRY EYE DISEASE?

a. Microbiological involvement
b. Inflammation
c. Environmental sensitivities (allergies)
d. Autoimmune disorders

9. WHICH OF THESE TREATMENTS (OTHER THAN ARTIFICIAL TEARS) DO THE PANELISTS SUGGEST CLINICIANS USE AS QUICKLY AS POSSIBLE?

a. Gels
b. Punctum plugs
c. Surgery
d. Anti-inflammatory therapy

10. MRS. JONES IS AN 80-YEAR-OLD WOMAN WHO HAD CATARACT SURGERY IN HER RIGHT EYE. SHE NOW PRESENTS WITH COMPLAINTS OF BLURRY VISION AND ITCHING IN THAT EYE, AND A DIAGNOSIS OF DRY EYE IS CONFIRMED. WHAT IS THE MOST LIKELY CAUSE OF HER DRY EYE SYMPTOMS?

a. Undiagnosed dry eye before cataract surgery
b. Preservatives used on the surface of the eye during surgery
c. Trauma to the lenticules during surgery
d. Failure to remove all the ophthalmic viscoelastic device during surgery

Individualized Management of Patients With Dry Eye Disease Part 1

Dry eye disease (DED) is a complex, multifactorial disorder that adversely impacts patient quality of life and daily functioning. DED has significant prevalence worldwide, affecting upwards of 25% of patients 65 years of age and older, although prevalence may be as high as 75%.[1-5]

Clinicians remain challenged with both the diagnosis and best treatment options for DED because, to date, multiple causes of the disorder have been identified.[4] *It is acknowledged that the two types of DED—aqueous-deficient and evaporative—have differing underlying etiologies and there is no "one size fits all" treatment. It also is acknowledged that meibomian gland dysfunction (MGD) is the most common cause of evaporative DED but mixed conditions are very common.*[4] *Confounding the issue further, many cases of DED go undiagnosed,*[6] *and once a diagnosis is made, treatment must be tailored to the individual and their disease type to be successful.*

For those who specialize in treating DED, there is agreement that early diagnosis and intervention can slow the progression of the disorder (and may be able to reverse disease progression).[7] *However, the severity of patient-reported symptoms coupled with clinical observation has traditionally been the primary means to determine a treatment strategy.*[8]

Furthermore, this is a costly disease. In 2016 McDonald et al[9] *evaluated the economic and humanistic burden of DED across Europe, the United States, and Asia. They suggested the true cost of DED would be substantially higher than evaluated studies suggest, "given the widespread use of over-the-counter artificial tears by individuals with DED symptoms."*[9] *Brown et al suggested the annual cost of artificial tears is US$96 per patient,*[10] *but Gayton et al estimated it closer to US$320 per person.*[11]

For as much attention as researchers pay to this disease, the underlying causes of DED are still not well understood and there has been some suggestion that DED may be associated with ocular surface inflammation.[12] Cataract & Refractive Surgery Today Europe *convened several leading authorities on the topic to discuss the mechanisms of action of DED and its prevalence, as well as how to effectively evaluate the signs and symptoms in order to make a diagnosis and develop a tailored treatment plan.*

—Professor Christophe Baudouin, MD, PhD, FARVO, Moderator

DEFINING DED

PROF. CHRISTOPHE BAUDOUIN: In 2017, the Tear Film and Ocular Surface Dry Eye Workshop II (TFOS DEWS II) was published, updating its 2007 publication. The updated report included a new definition of DED and new a classification scheme.[2] The new definition is as follows:

"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[2]

The new TFOS-DEWS classification scheme is now based on the predominant and often overlapping etiologies of aqueous deficient and evaporative dry eye. Importantly, based on new data, neurosensory abnormalities were included in the definition for the first time.

Q | What is your opinion of the new definition and classification scheme? Do you find it suitable and useful?

PROF. STEFANO BARABINO: There are clearly different definitions of dry eye according to the literature. We know there are two types: aqueous-deficient and evaporative. Both have different underlying etiologies; therefore it is critical to distinguish between them to make a proper diagnosis.

Dry eye is no longer considered a disorder of the tear film caused by a lack of tears or excessive tear evaporation; it is now recognized as a disease of the ocular surface (Figure). Of course, the tear film plays an important role, but is it not the only factor—you also have to consider inflammation and eyelid and blink abnormalities. No two patients are alike, and there are different pathogenetic factors playing a role. In some patients, inflammation is clearly the main driver of DED, but in other patients that inflammation is not as pronounced. When we diagnose DED, we should consider all these factors.

PROF. BAUDOUIN: Should inflammation be considered the primary mechanism, the secondary mechanism, or both?

PROF. BARABINO: If you look at the literature, it is not clear which comes first. But certainly, inflammation could be the consequence of increased osmolarity, as Pflugfelder et al established.[13]

PROF. MARGARITA CALONGE: DED is not only a disease of the ocular surface, but a disease of the lacrimal functional unit.[14] Stern et al reported that chronic inflammation of the lacrimal functional unit leads to reduction in tear film integrity and the ability of the ocular surface to adapt to environmental factors. DED compromises the ocular surface, all the lacrimal glands, including the meibomian glands and conjunctival and corneal secreting cells,

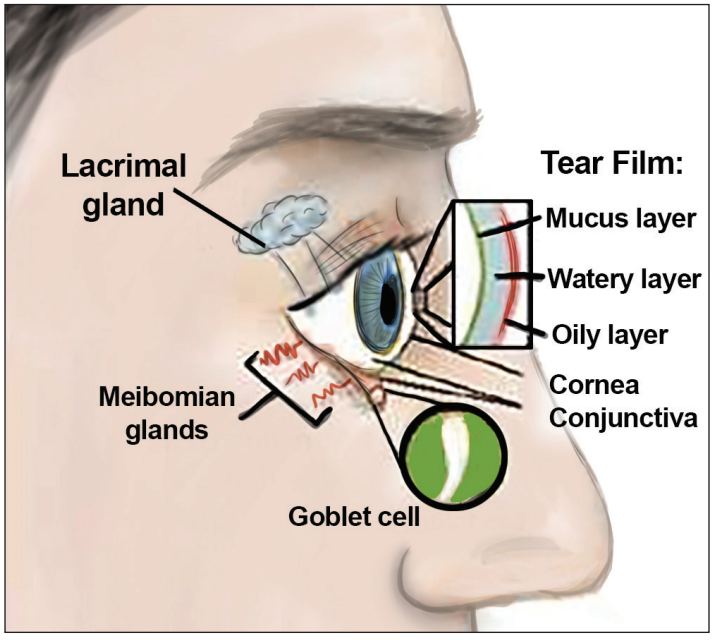

Figure. There are different pathogenetic factors that play a role in DED.

and the neurohormonal regulatory system. This is a much more comprehensive picture of DED than what we had in the past.

We need to remember that inflammation is the mechanism that the body, our organism, uses to defend itself from injuries of any kind: traumatic and infections, among others. I would be very surprised if inflammation were not the pathogenetic mechanism, regardless of the initial cause. To me, the first thing we must address is inflammation, after addressing all the cofactors that may be having an influence in each particular case. If we get rid of inflammation, the lacrimal-producing cells will be able to function much better because they are not surrounded by inflammatory cells.

PROF. BAUDOUIN: Is there an interest in measuring hyperosmolarity, as it is included in the definition? Do you think hyperosmotic stress can be used to diagnose individuals or to discriminate between different subcategories? Or there is still a lot of work to be done in order to have an effective marker of the stress?

PROF. ELISABETH MESSMER: I think the concept of hyperosmolarity causing inflammation makes a lot of sense. This has been proven in cell cultures and in animal studies.[15-17] Moreover, both, hyperosmolarity and inflammation may be used as important biomarkers in diagnosing DED in the future.

The problem is we don't have the perfect instruments to measure osmolarity in the eye and we're measuring osmolarity in the wrong spot, the tear meniscus. What we really need to do is measure osmolarity at the corneal surface, but currently we have no way of doing so.

Right now, the TearLab Osmolarity System and i-Pen Tear Osmolarity System are on the market for measuring osmolarity. The TearLab system measures nanoliter volumes of tear fluid from the inferior lateral tear meniscus with the same analytical performance as laboratory osmometers.[18] The i-Pen System is a hand-held electronic diagnostic device that measures at the tarsal conjunctiva. Like the TearLab product, its results are reproducible. After about 5 seconds of eyelid tissue contact, the i-PEN displays a quantitative tear osmolarity test result on its display.[19]

It will be very interesting in the future to find out which technique performs better, the one measuring in the tear meniscus or the one measuring at the tarsal conjunctiva.

It is important to measure osmolarity. We know osmolarity is highest in patients with severe DED. In those patients, however, we may not need osmolarity for diagnosis. In my opinion, osmolarity testing might be better served as a biomarker for mild to moderate DED in the future.

PROF. BAUDOUIN: In the new TFOS definition of DED, the concept of visual impairment and the impact the disease has on visual function has disappeared. I think this is a mistake. People with DED have unstable, poor vision, and they tend to overcompensate for it. This overcompensation induces visual fatigue. Do you agree with the removal of visual impairment from the definition?

PROF. BARABINO: Measuring visual function is very important. In patients with DED visual acuity could reach 20/20, but the quality of vision can be altered. This has been clearly demonstrated with contrast sensitivity test[20] and wavefront aberrations as reported by Koh et al.[21] Patients have difficulty reading and using computers, which may impact professional productivity. They also report difficulty driving, in both daylight and at night, as well as difficulty watching television.[22,23] Taken together, DED symptoms can significantly impact patient quality of life and patients frequently become frustrated with their treatments and repeatedly visit clinicians looking for treatment alternatives.

PROF. BAUDOUIN: That is absolutely true and important to recognize. DED is not just a stinging eye or itching eye. It is an eye that is impaired in numerous ways, including vision.

DIAGNOSING DED

Q | **PROF. BAUDOUIN:** There are two different categories of DED: aqueous deficient and evaporative. What are the differences between the two, and how are they diagnosed?

PROF. CALONGE: In my experience, clinicians do not agree on what typical DED looks like. The prototypical DED patient has aqueous-deficient dry eye with corneal staining and low Schirmer results. However, most patients have a normal, or somewhat normal, Schirmer test, and they still complain about dryness, itching, burning, and a gritty, foreign-body sensation in their eyes. It is difficult to weigh those symptoms with a Schirmer result of 10, 8, or 5 if we only think as dry eye as a problem of lack of tears.

We need to think of DED in terms of the quality of the tear film and not just the quantity. I tell my patients that DED can be caused by insufficient or poor quality tears, so that they understand that

they can have DED with normal tear production. An altered composition of the tear film is still the most common type of DED in my opinion. And the most frequent cause, but not the only one, is MGD, additionally caused by several underlying diseases.

PROF. BAUDOUIN: You have developed the Controlled Environment Laboratory (CELab) for studying DED, which is unique in Europe. It controls the adverse environment that reproduces the condition of dry eye in relation with the environment. Is your technique able to discriminate, more or less, aqueous deficiency compared with tear instability? Or is it just a way to increase the level of dry eye, whatever the mechanism?

PROF. CALONGE: The problem with conventional DED clinical trials is that patients are exposed to different environmental conditions that impact their symptoms. The ocular surface of each patient is challenged differently.[24] CELab was developed to solve this problem and challenge each ocular surface in each patient in the same way. It stabilizes patients in an environmental chamber so that all the measurements can be taken in the same level of humidity, at the same temperature, and within the same air movement. It also creates an inflammatory state by putting patients under desiccating stress, including low humidity and low air movement, which causes inflammation.[25,26] These experimental conditions are very useful to see if therapeutic drugs can not only treat DED in conventional situations but can also prevent patients from getting worse in indoor conditions such as cars, planes, shopping centers, and, of course, our offices. In these environmental conditions, "normal" and "adverse," dry eye patients are thoroughly evaluated so that a potential drug for DED can show its therapeutic signals that can be later selected as endpoints for therapeutic multicenter trials.

PROF. BAUDOUIN: What role do screens play in the development of DED? Are smartphones, computers, and tablets causing DED because of an overexposure to blue light?

PROF. MESSMER: In the past, my typical DED patient was a woman older than 50 years with aqueous deficiency. Now, I'm seeing more instances of evaporative dry eye in much younger patients, including men. This is very unusual, and there must be a reason. Most of these people are working in typical office conditions on a computer. When they get home, they use other displays including phones or watch TV. We still don't quite understand the role blue light and screens are playing in the development of DED, but studies have shown a correlation. For example, a study of 916 children in South Korea found that smartphone use was strongly associated with pediatric DED.[27] Other studies have found strong correlations between 8 hours of computer use and dry eye symptoms in university students.[28-31]

Other clinicians are noticing the change in DED patients as well. A 2016 National Eye C.A.R.E Survey found that 9 out of 10 eye care professionals believe a multiscreen lifestyle is responsible for the rise in DED and that the condition is becoming more common. Further, 76% of eye care professionals surveyed are seeing an increase in patients between the ages of 18 and 34.[32]

"Some studies have found that dry eye-like symptoms can occur in up to a third of people postcataract surgery.[42,43]"

— Prof. Barabino

PROF. BAUDOUIN: Our Japanese colleagues have developed a theory that blue light may cross-react and interact with an unstable tear film causing diffusion of the light. This could be one mechanism by which the quality of vision is impaired, even in patients with only tear instability.[33] This causes a series of symptoms such as decreased vision and ocular fatigue. Do you agree that, in the future, we should expect to see more patients with dry eye due to blue light and screen exposure?

PROF. BARABINO: Yes, it is really becoming a problem, especially in younger people. Overexposure to light may be one reason why we are seeing more patients, especially among teenagers. Another factor to consider is that when we are using a screen, we have more incomplete blinks than when reading on hardcopy. Studies have shown that the number of blinks per minute are largely the same between computer and hardcopy use (14.9 vs 13.6 blinks per minute, respectively).[34] However, computer users had a higher percentage of incomplete blinks, which may be associated with visual fatigue.

PROF. BAUDOUIN: We know LASIK surgery can exacerbate dry eye and that outcomes postoperatively are worse in patients identified preoperative with DED than in patients without DED preoperatively.[35-39] The American Academy of Ophthalmology now considered uncontrolled DED a contradiction for LASIK.[40] The transection of the corneal nerve after LASIK may strongly influence recovery of the tear secretion and can cause of chronic inflammation, leading to dry eye symptoms.[41] What about dry eye post-cataract surgery? What are the mechanisms at play that cause us to see more patients with dry eye after cataract extraction?

PROF. BARABINO: Some studies have found that dry eye-like symptoms can occur in up to a third of people postcataract surgery.[42,43] What I have observed in patients after cataract surgery is the lack of stability of the tear film. We measured the tear break-up time and demonstrated that the break-up time goes back to the previous surgery values 3 months post-surgery. Tear film instability can be caused by many different things. It may be caused by using

"Chalmers et al have shown that the patients' self-assessment of dry eye symptoms is consistently more severe than what treating clinicians perceive."

—Prof. Calonge

preservatives on the surface of the eye. It may also be caused by what we use to sterilize the ocular surface before surgery. Another theory is that surgery incudes trauma to the orbicular muscles, which leads to incomplete blinking postoperatively. There are many different reasons, including the nerve cut at the temporal site of the cornea. I do not have a definitive answer, and there are many different factors that can induce dry eye-like symptoms.

PROF. CALONGE: I am personally curious as to why this is an issue postcataract surgery now when it wasn't in the past. The only thing I can think of is that modern-day cataract surgery is being done under topical anesthesia instead of the deep anesthesia that we used in the past. This might account for why we are not only seeing dry eye symptoms but chronic, neuropathic pain. But we really do not know.

I have some experience seeing dry eye symptoms and/or severe neuropathic pain after refractive surgery. We are working on a study that is enrolling patients from all over the country to study this problem. There are many variables at play, and hopefully in a couple of years, we will have some answers as to why some patients develop dry eye symptoms and/or pain postoperatively and others don't.

PROF. BAUDOUIN: You raised an interesting issue regarding neuropathic pain. What do we know about the development of neuropathic pain? Is there any way to detect patients at high risk for developing pain and dry eye symptoms postoperatively?

PROF. MESSMER: Trattler et al found that many patients undergoing cataract surgery have undiagnosed, unrecognized dry eye before surgery.[6] This is an important message. Clinicians need to look for, diagnose, and treat DED before surgery to reduce postoperative issues.

PROF. BAUDOUIN: At my institution, Alexandre Denoyer, MD, PhD, and I performed an interesting study comparing the rate of dry eye at 6 months between standard LASIK and small incision lenticule extraction (SMILE).[44] We found a lower rate of dry eye if the incision is smaller, which means that the transection of the nerve plays a role. The corneal nerve plays a role in either causing dysregulation of the ocular surface or lacrimal function of the unit, or conversely, causing neuropathic stimulation and what we call neuropathic pain. What are the best ways to assess the symptoms and how to address symptoms that develop?

PROF. CALONGE: There are many dry eye questionnaires,[45-52] but we do not have a single questionnaire that is good enough. For example, we have the Ocular Surface Disease Index (OSDI),[45,49] a 12-item scale that assesses DED symptoms and how they impact vision. There is the Symptom Assessment iN Dry Eye (SANDE),[53,54] which also measures dry eye symptoms but using only two questions. A study by Amparo et al found that there was a statistically significant correlation between the two questionnaires, but that there are clear advantages to having patients only answer two questions as opposed to 12.[55] OSDI didn't offer enough additional information to justify having the patient answer so many additional questions.

Along with Dr. Steven from Cologne in Germany, we developed a new questionnaire that has only one question with three possible answers, in part, because patients are confused by having to answer so many questions. I have found a lack of correlation between what patients answer in the questionnaires and their responses when I ask them later in my office without questionnaires in between. Chalmers et al have shown that the patients' self-assessment of dry eye symptoms is consistently more severe than what treating clinicians perceive.[56] In their cross-sectional observational study,[56] 162 patients with dry eye and 48 controls were recruited from clinical databases of ICD-9 codes in six clinical sites. Before examination, patients self-assessed the severity of their dry eye symptoms from none to extremely severe. After a clinical examination that included dry eye tests, the clinician discussed patient symptoms and then rated their dry eye from none to severe. Researchers did find a correlation and agreement between clinicians and patients, but clinicians underestimated the severity in more than 40% of patients by at least 1 grade.

This tells me that we need better, more quantitative tools to assess dry eye-related symptoms. We need to simplify our questionnaires. This is very difficult because there is nothing more subjective than a patient's pain and related dry eye symptoms. It is a mistake that we have to base the approval of our therapies on something so subjective.

PROF. BAUDOUIN: The discrepancy between signs and symptoms of DED is a major barrier to diagnosing these patients. Some patients complain a great deal about dry eye symptoms, but we don't understand why because their eyes look healthy upon examination. And some patients complain very little despite having a severely damaged cornea. I have found for some of my patients that their cornea is so damaged they cannot discern dryness symptoms. How do you approach patients who describe dry eye symptoms but seem to have no keratitis upon examination? Do you think tear instability really causes dry eye? What about neuropathic pain—do we believe neuropathic pain is truly a dry eye?

PROF. BARABINO: It is very difficult to diagnose the stage of dry eye that we have in front of us when the patient first presents. In the beginning stages of DED, I have had patients with DED complain a lot about neuropathic pain but in whom there are no signs of ocular surface damage. It could be that the neuropathic pain is the first step on the dry eye pathway. Conversely, some patients come in who are at the end of this pathway. They do not complain about neuropathic pain because they are past that stage. The issue is determining at what stage the patient is along the pathway. We do not currently have tools to understand the history of DED or to accurately measure corneal sensitivity in the everyday practice.

PROF. BAUDOUIN: Regarding neuropathic pain, we have been working with different experimental models and have identified different approaches.[57] One is some kind of allodynia, which means that the receptors transmit a pain response to normally benign stimuli. Normally cold receptors are stimulated in an innoxious manner by the thinning of the lacrimal film to induce blinking, but if continuously stimulated cold receptors may cause pain or discomfort sensations and stimulate neurogenic inflammation. Another way to understand neuropathic pain is through what we call central sensitization. It means that when there is chronic pain related to corneal involvement and stimulation, the trigeminal centers in the brainstem that bring the information from the trigeminal nerve have continuous activation. This results in pain symptoms even though the cornea appears normal or has recovered from former damage. Therefore, a patient should be pain-free at this stage but is still suffering. This is central sensitization that results from activation of microglial cells in the trigeminal pathway.[58,59]

PROF. CALONGE: Postrefractive surgery patients are some of the most symptomatic patients I have ever seen. They have apparently normal-looking corneas at the slit lamp and no staining, but their symptoms are horrible. If there are symptoms, there have to be signs somewhere, we just cannot see them at the slit lamp. But something has to explain why patients are so symptomatic. We just haven't found it yet. The in vivo confocal microscope will probably give us some answers in the future.

PROF. BAUDOUIN: What is your preferred test to diagnose DED? We currently have five available to all of us: Schirmer, fluorescein staining, break-up time, lissamine green, and tear osmolarity.

PROF. BARABINO: If I had to choose, I would choose fluorescein testing. By using fluorescein you can measure tear break-up time, which will provide the clinician with information on tear stability. You can also use a yellow filter on the slit lamp, which allows you to clearly see the damage at the cornea and the conjunctiva. Patients with a history of chronic dry eye most often have damage at the conjunctiva.[60]

PROF. CALONGE: I agree that fluorescein is very effective. If I had to pick one, it would be corneal fluorescein staining, although knowing that it is not ideal, as it is also influenced by environmental conditions. Schirmer is useful as well. I used to complain a lot about the reliability of Schirmer, but I have found that low Schirmer scores (under 4 to 5 mm) are actually quite reliable. Conversely, scores higher than 5 to 6 mm do not help much. Conjunctival staining is also very useful and often underestimated. The problem is that rose bengal is very irritative and many patients do not tolerate it. The other option, lissamine green, does not have the EU mark and cannot be used in the clinical setting, only under investigational settings. Tear break-up time is also useful but in my experience it is quite low in asymptomatic elderly patients; for instance, to find normal controls who have break-up times higher than 5 to 7 seconds is very difficult. We use tear osmolarity in clinical trials.

"By using fluorescein you can measure tear break-up time, which will provide the clinician with information on tear stability."

— Prof. Barabino

PROF. BAUDOUIN: I also prefer fluorescein testing for exactly the same reasons: corneal staining is the most important criterion for dry eye, with useful existing scoring systems, and the break-up time, if short indicates tear instability. The shape and timing of break-up can also be very informative to assess: immediate break-up rather indicates mucin deficiency whereas later random break-up is more in favor of evaporation due to lipid deficiency. The conjunctiva can be easily examined with fluorescein as well; it is not necessary to have other staining. And don't forget that the superior and nasal conjunctiva, the limbus—especially superiorly—need to be addressed. We can observe superior limbic keratoconjunctivitis, something that is typical with severely symptomatic patients. The cornea looks almost normal or just with tear instability but in reality, the patient has significant staining in the superior limbus and conjunctiva.[61] It is quite common if you look for it carefully.

PROF. MESSMER: I would also select fluorescein because you can see the tear meniscus as measure of tear production, analyze tear break-up time as a measure of tear stability and do corneal staining with fluorescein to demonstrate corneal damage, all in one examination. In addition, conjunctival staining can be visualized with fluorescein, thus making lissamine green and rose bengal dispensable for routine examinations. Schirmer test is an important test for me to be performed early in the care of the patient to judge severity of DED, as a Schirmer test less/equal than 5 mm/5 minutes indicates severe dry eye and makes me watch this patient more closely.

"I agree that the confocal microscopy gives information that is absolutely important in some cases."

— Prof. Baudouin

PROF. BAUDOUIN: How do you go about differentiating aqueous deficiency from tear instability?

PROF. CALONGE: MGD is extremely common in patients with Sjogren syndrome. Most of my patients, if not all of them, have at least moderate if not severe posterior blepharitis. It is a completely overlapping field.

LATEST TREATMENTS AND TECHNOLOGIES

Q | PROF. BAUDOUIN: There are a number of new technologies available for diagnosing of DED such as LipiView, the TearLab Osmolarity System, confocal microscopy, OCT, the Oculus Keratograph for measuring tear stability, and the Optical Quality Analysis System (OQAS) to address the quality and stability of the vision. In your experience, how useful are these different techniques? Which are the must-haves in the clinic?

PROF. MESSMER: These techniques are interesting in terms of developing a diagnosis, but they are also very important for communicating with patients. It is only with these new instruments that we get data, colorful pictures, and numbers. It gives us something to clearly illustrate to the patient what's wrong and what needs to be corrected. For the diagnosis of MGD, we measure the lipid layer with interferometry and examine the anatomy of the meibomian glands directly with meibography. It is very important to see where we stand and whether the disease worsens over time.

PROF. BAUDOUIN: Do you think the morphology of the meibomian glands reflect the functionality of the lipid layer and the functionality of the glands? That it correlates more or less?

PROF. MESSMER: In my patients, it correlates more or less. But as always in dry eye, signs and symptoms as well as different examinations do not correlate well with each other. There may be patients with mild disease and a major loss of glands and vice versa. In most of my patients, the clinical picture, the lipid layer, and the meibomian glands, however, correlate quite well.

PROF. BARABINO: I think it is very important to measure the tear break-up time. We can have numbers and a report to explain the situation to the patient. At the same time, however, we have to be careful and critical with the results we obtain. The other thing that I find interesting is confocal microscopy. With confocal microscopy, we can see if symptoms are caused by an activation of the dendritic cells in the cornea and damage at the level of the corneal nerve. This is very important when we screen patients before refractive surgery. Most of my potential refractive surgery patients are typically long-term contact lens wearers. Some are patients with blepharitis, which can induce a change of the ocular surface. All of these situations can activate the immune cells in the cornea. We need to be extra careful when performing refractive surgery on these patients to ensure we don't induce complications.

PROF. BAUDOUIN: I agree that the confocal microscopy gives information that is absolutely important in some cases. Confocal microscopy is really a histology-like assessment. Sometimes this is the only technique that allows us to find an infiltration with inflammatory cells. Sometimes we can also observe abnormality of the nerves and abnormality of the basement membrane.[62] Epithelial basement membrane dystrophy (EBMD) causes the instability of the epithelium. Of course, EBMD is not exactly dry eye because it is closer to recurrent corneal erosion syndrome. But, recurrent corneal erosion syndrome is often associated with some condition of dry eye as an abnormal tear film over an unstable epithelium may be an important factor causing recurrences of erosion.

PROF. CALONGE: My challenge with confocal microscopy is that it is somewhat time consuming. The images need time to be processed through the software. We can't use it to make quick decisions in clinical practice. But it is an extraordinary tool in clinical studies and trials and for thise aims, we use it all the time.

PROF. BAUDOUIN: OCT doesn't have a resolution that is sufficient to replace confocal microscopy, but if we could have a high-resolution OCT in the future, this would very useful for morphology.

Let us now move onto biomarkers. These are objective indications of a medical state observed outside the patient that can be measured both accurately and reproducibly.[63] What are the panel's thoughts about biological biomarker testing for DED? How close are we to the development of biological biomarkers that could help in the diagnosis of DED?

PROF. CALONGE: We are getting closer little by little, but this technology is still under investigation. I think it is becoming more and more useful for clinical trials, in which we can define disease severity, inflammatory activity and therapeutic biomarkers. But this cannot be done in the clinic setting, at least not yet. Gathering tears is simple, quick, and inexpensive. But then to measure 30 cytokines in 1 µL of tears or performing proteomics in 2 µL—which I find amazing—that has to be done with expensive machines and well-trained technicians and researches. There are some other groups around the world working on this, and I am hoping we will have something ready for clinical practice in 5 to 10 years.

"The typical step-wise approach does not work when signs and symptoms do not correlate."

—Prof. Messmer

There is the InflammaDry, which is a disposable, low-cost test that detects elevated levels of matrix metalloproteinase 9 (MMP-9), an inflammatory marker, but it is not quantitative.

PROF. MESSMER: Companies start to realize how important biomarkers are and how big the market is for such instruments. And as far as I know, there are many companies developing such techniques. But I think we are a few years from having a practice tests that allow us to evaluate biomarkers in every patient. There is also the matter of reimbursement. These biomarker tests are quite expensive, and—at least at the moment—insurance companies are not routinely paying for these extra examinations. Therefore, I think there's another step that has to be taken to get biomarker evaluations into every clinical practice in many countries. And that step has to come from governments and health care policies.

PROF. BARABINO: I think that today, the instruments that we have to measure cytokines or markers of inflammation are restricted to research only. The application in practice is still far away. InflammaDry is the only instrument that we can use and its application is extremely limited because it is not quantitative, as Prof. Calogne noted. I am looking forward to having these tests in every day practice because diagnosing inflammation on the surface of the eye is very important.

PROF. BAUDOUIN: If we could develop a biomarker that was inexpensive, quick to perform, and reimbursed, what would you use it for? What is the most important question the biomarker test could address? Is it the severity of dry eye, inflammation, microbiological involvement, allergies? What would be the most useful?

PROF. BARABINO: I would want a biomarker to diagnose inflammation. If I can diagnose inflammation in everyday practice, that will change my therapeutic approach. I can differentiate between dry eye and allergies in other ways. I think tear osmolarity is important, but I do not base my treatment on osmolarity. So, to me, the most important question that needs answering is whether or not there's inflammation. And if there is, what is the degree of the inflammation on the patient's ocular surface?

PROF. BAUDOUIN: If you were able to identify inflammation, you could propose an anti-inflammatory or immunomodulating strategy to treat the symptoms and provide symptom relief. For example, if a patient has an inflammation on the ocular surface before surgery, you would clearly treat that before recommending the patient undergo surgery.

PROF. MESSMER: Yes. My preference is also a biomarker for inflammation; you could do two jobs at once. If you selected the correct inflammatory markers, you could differentiate between inflammation from dry eye and inflammation from other ocular disorders such as allergies.

PROF. CALONGE: I agree; I would say inflammation, too. I would like to add that we often underestimate our role as physicians and the most important diagnostic tool that we have: patient history. If we know what questions to ask, we should be able to differentiate between dry eye, allergies, and so forth; and there is not a biomarker that can make up for a well done clinical history and thorough evaluation. We need biomarkers for the issues that we are unable to see with our slit lamp.

DED TREATMENT

Q | **PROF. BAUDOUIN:** The TFOS DEWS II proposed a step-wise approach to treating DED in accordance with the severity of the disease.[64] For mild DED, the group recommends a tear substitute. For DED that is a little more severe, the group recommends a gel. From there, the group recommends an immunomodulating agent. Finally, for patients with the most severe DED, TFOS DEWS II recommends autologous serum, amniotic membrane, or surgery. Moshirfar et al[1] proposed a similar step-wise approach when initiating treatment with artificial tears, although we may not have all of those options available in each of our countries.
Is everyone comfortable with a step-wise approach? Should we restrict antiinflammatory eye drops to patients with severe cases of DED? Is there any interest in using antiinflammatory drops in less severe cases? Finally, do you think severity assessment is reliable?

PROF. CALONGE: I tend to start using antiinflammatory therapy as soon as I can; the earlier the better. I use this type of therapy on patients who haven't had success with multiple artificial tears and lubrication at night. To me, this means that I have to use antiinflammatory therapy, assuming the problem is inflammation in the conjunctiva and tear-producing glands. If we don't transition to anti-inflammatory therapy at this point (after the patient has been found refractory to artificial tears), their disease will progress.

PROF. BARABINO: I like the step-wise approach in treating patients with DED. I also use antiinflammatory treatments as soon as I can. I think it is very important to prevent DED from becoming a chronic disease. When ocular surface immune mechanisms are activated, dry eye could become chronic and therefore very difficult to treat.

We must be dynamic in treating our patients. Maybe patients at a certain stage need antiinflammatory treatment, and once that treatment is successful they can transition back to artificial tears or vice versa. We have to change treatments as the disease changes based on the clinical features and patient-reported symptoms. And of course, every patient is different. We cannot have a standard treatment; there is no one-size-fits-all approach.

PROF. MESSMER: The typical step-wise approach does not work when signs and symptoms do not correlate. There may be some other important factors that need to be addressed such as central sensitivity, neuropathic pain, or even psychological problems. There may be a subclinical disease causing the symptoms, but we can't see the signs yet. I would try to use the normal step-wise approach in these patients as well. But we may need some other treatment, such as painkillers or psychotherapy in these patients, to fully address the problem.

PROF. BAUDOUIN: The psychological impact of DED is very high. Conversely, a patient who is depressed from chronic symptoms will have a poor quality of life. It is all tied together. Would it be useful to have a specific medication that could be more powerful for symptomatic patients in the future? Should we be researching and developing that?

PROF. MESSMER: Yes. There are studies under way at the moment that analyze substances that act against the pain receptors in the cornea.

So, there are substances available and there are studies under way to address those patients who have a major symptom but not many signs. I think it is a very interesting approach, especially when we consider the neurosensory changes we're having, which are also in the new definition of dry eye. I'm hopeful that a new group of therapies will be developed in the future.

PROF. BAUDOUIN: Thank you for your thoughtful insights, observations, and recommendations. It has been a pleasure working with you. ■

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INDIVIDUALIZED MANAGEMENT OF PATIENTS WITH DRY EYE DISEASE - PART 1

Release Date: July 2018
Expiration Date: July 2019

INSTRUCTIONS FOR CME CREDIT

To receive *AMA PRA Category 1 Credit™*, you must complete the attached Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: +1 (215) 933-3950. To answer these questions online and receive real-time results, please visit evolvemeded.com and click "Online Courses." If you are experiencing problems with the online test, please email us at support@evolvemeded.com. Certificates are issued electronically; please be certain to provide your email address below.

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Full Name _____ ❑ MD/DO participant ❑ non-MD participant

Phone (required) _____ ❑ Email (required) _____

Address/P.O. Box _____

City _____ State /Country _____ Zip/Postal Code _____

License Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this activity)
___ 0
___ 1-5
___ 6-10
___ 11-15
___ 15-20
___ 20+

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

Training of Fellows ___ Yes ___ No

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Discuss the mechanism of action of dry eye disease.	_____	_____	_____
Evaluate the signs and symptoms in patients with dry eye complaints.	_____	_____	_____
Discuss the prevalence of dry eye disease.	_____	_____	_____
Develop a differential diagnosis for patients with complaints of dry eye.	_____	_____	_____

POSTTEST QUESTIONS

1. **PLEASE RATE YOUR CONFIDENCE ON YOUR ABILITY TO APPLY UPDATES IN THE MANAGEMENT OF DRY EYE DISEASE IN THE CLINIC BASED ON THIS ACTIVITY. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT.)**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **PLEASE RATE HOW OFTEN YOU INTEND TO APPLY ADVANCED DRY EYE DISEASE MANAGEMENT IN THE CLINIC. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS.)**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

3. **THE 2017 TEAR FILM AND OCULAR SURFACE DRY EYE WORKSHOP II REVISED THE DEFINITION OF DRY EYE DISEASE IN ALL THE FOLLOWING WAYS EXCEPT:**
   a. It created a new classification scheme of dry eye disease.
   b. It excluded neurosensory abnormalities from the definition of dry eye disease.
   c. It recognizes the multifactorial nature of dry eye as a disease where loss of homeostasis of the tear film is the central pathophysiological concept.
   d. It removed visual impairment and the impact the disease has on visual function from the definition.

4. **THE FOLLOWING ARE SYMPTOMS OF DRY EYE DISEASE EXCEPT:**
   a. Itching, burning eyes
   b. A gritty, foreign-body sensation in the eyes
   c. Glare, starbursts, or halos
   d. Neuropathic pain

5. **IDENTIFY THE POPULATION OF PATIENTS IN WHICH DRY EYE DISEASE IS BECOMING MORE PREVALENT.**
   a. People aged 18 to 34
   b. Postmenopausal women over age 50
   c. Women aged 34 to 50 with autoimmune diseases
   d. Men aged 35 to 50 who have had refractive surgery

6. **THE PREFERRED DIAGNOSTIC TEST FOR CONFIRMING DRY EYE DISEASE IS _____ .**
   a. Schirmer test
   b. Lissamine green
   c. Tear osmolarity
   d. Fluorescein

7. **THE _____ IS CONSIDERED USEFUL TECHNOLOGY IN THE CLINIC FOR HISTOLOGIC EXAMINATION OF THE OCULAR SURFACE.**
   a. LipiView
   b. TearLab Osmolarity System
   c. Confocal microscope
   d. Keratograph

8. **ACCORDING TO THE PANELISTS, WHAT SHOULD BE THE IDEAL BIOMARKER FOR DRY EYE DISEASE?**
   a. Microbiological involvement
   b. Inflammation
   c. Environmental sensitivities (allergies)
   d. Autoimmune disorders

9. **WHICH OF THESE TREATMENTS (OTHER THAN ARTIFICIAL TEARS) DO THE PANELISTS SUGGEST CLINICIANS USE AS QUICKLY AS POSSIBLE?**
   a. Gels
   b. Punctum plugs
   c. Surgery
   d. Anti-inflammatory therapy

10. **MRS. JONES IS AN 80-YEAR-OLD WOMAN WHO HAD CATARACT SURGERY IN HER RIGHT EYE. SHE NOW PRESENTS WITH COMPLAINTS OF BLURRY VISION AND ITCHING IN THAT EYE, AND A DIAGNOSIS OF DRY EYE IS CONFIRMED. WHAT IS THE MOST LIKELY CAUSE OF HER DRY EYE SYMPTOMS?**
    a. Undiagnosed dry eye before cataract surgery
    b. Preservatives used on the surface of the eye during surgery
    c. Trauma to the lenticules during surgery
    d. Failure to remove all the ophthalmic viscoelastic device during surgery

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this continuing medical education (CME) activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____ No

I plan to make changes to my practice based on this activity. _____ Yes _____ No

Please identify any barriers to change (check all that apply):

_____ Cost

_____ Lack of administrative support

_____ Lack of time to assess/counsel patients

_____ Reimbursement/insurance issues

_____ Patient compliance issues

_____ Other. Please specify: _____

_____ Lack of consensus or professional guidelines

_____ Lack of experience

_____ Lack of opportunity (patients)

_____ Lack of resources (equipment)

_____ No barriers

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the ACCME) that were enhanced through your participation in this activity:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____


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