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CANADIAN JOURNAL *of* OPTOMETRY | REVUE CANADIENNE D'OPTOMÉTRIE

SPECIAL SUPPLEMENT

NATIONAL DRY EYE DISEASE GUIDELINES FOR CANADIAN OPTOMETRISTS

Screening, Diagnosis and Management of Dry Eye Disease:
Practical Guidelines for Canadian Optometrists

CANADIAN ASSOCIATION OF OPTOMETRISTS
ASSOCIATION CANADIENNE DES OPTOMÉTRISTES

CANADIAN JOURNAL *of* OPTOMETRY
REVUE CANADIENNE *d'*OPTOMÉTRIE
Vol. 76, Suppl. 1
2014
ISSN 0045-5075
The *Canadian Journal of Optometry* is the official publication of the Canadian Association of Optometrists (CAO) / La Revue canadienne d'optométrie est la publication officielle de l'Association canadienne des optométristes (ACO) : 234 Argyle Avenue, Ottawa, ON, K2P 1B9. Phone 613 235-7924 / 888 263-4676, fax 613 235-2025, e-mail info@opto.ca, website www.opto.ca. Publications Mail Registration No. 558206 / Envoi de publication – Enregistrement no. 558206.
The Canadian Journal of Optometry / La Revue canadienne d'optométrie (USPS#0009-364) is published six times per year at CDN$55, and CDN$65 for subscriptions outside of Canada. Address changes should be sent to CAO, 234 Argyle Avenue, Ottawa, ON K2P 1B9.

AJP Andrew John Publishing Inc.
andrewjohnpublishing.com

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CANADIAN JOURNAL *of* OPTOMETRY | REVUE CANADIENNE D'OPTOMÉTRIE
EST. 1939 VOLUME 76 SUPPLEMENT 1

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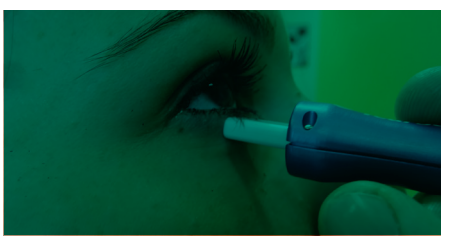

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Meibomian Gland Evaluator (TearScience) used to express the meibomian glands with a consistent force.

Screening, Diagnosis and Management of Dry Eye Disease: Practical Guidelines for Canadian Optometrists

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The Canadian Dry Eye Disease Consensus Panel was developed to create a national guide for the clinical management of dry eye disease in an effort to assist Canadian optometrists in the diagnosis and management of one of the most prevalent ocular diseases they will encounter. The panel consists of experts from multiple areas of optometry including private practice, academia and research. Experts were chosen based on their clinical acumen in the field of dry eye disease management, publication frequency, clinical research and recommendations from Canadian colleagues citing their expertise in this area of practice. Due to Canada's vast geographical area, experts were chosen from different regions of the country. The West Coast, Prairies, Ontario, Quebec, and the Maritimes were all represented. Editorial support was provided by Paul Karpecki, O.D. and Derek Cunningham O.D., both of whom are Canadians who are involved in dry eye/surgical practices in the United States. Unrestricted educational funding was provided by Allergan Inc, Canada.

ABBREVIATIONS:

ALA = alpha-linolenic acid; CL = contact lens; CN7 = seventh cranial nerve/facial nerve; CTT = cotton thread test; DED = dry eye disease; DEQ = Dry Eye Questionnaire; DEQ-5 = 5-item Dry Eye Questionnaire; DHA = docosahexaenoic acid; EFA = essential fatty acid; EPA = eicosapentaenoic acid; FL-TBUT = fluorescein TBUT; GLA = gamma-linolenic acid; GPC = giant papillary conjunctivitis; IDEEL = impact of dry eye on everyday life; IOP = intraocular pressure; KCS = keratoconjunctivitis sicca; LWE = lid wiper epitheliopathy; LG = lissamine green; MG = meibomian gland; MGD = MG dysfunction; MMP = matrix metalloproteinase; NIBUT = non-invasive break-up time; NSAIDs = non-steroidal anti-inflammatory drugs; OCT = optical coherence tomography; OSDI = Ocular Surface Disease Index; PRTT = phenol red thread test; SLE = slit lamp exam; SLK = superior limbic keratoconjunctivitis; SPEED = standard patient evaluation of eye dryness questionnaire; SPK = superficial punctate keratitis; SS = Sjögren syndrome; TBUT = tear break-up time; TMH = tear meniscus height; ULMS = upper lid margin staining

INTRODUCTION

Dry eye Disease (DED) is one of the most common conditions encountered in optometric practice. The reported prevalence of this disease ranges from 7.8 to 29%.[1-5] These estimates vary depending on the definition of DED used, and the age of the cohort and country where the study was conducted. Regardless of the actual number, the appropriate diagnosis and management of this common disease is critical to meeting the eye care needs of a large segment of the general North American population. However, poor accessibility of eye care services, costs, as well as the restriction of existing treatment modalities to primary care practitioners are some of the reasons contributing to the lack of care in this population. Further, some consider DED to be a symptom rather than a disease and, consequently, fail to realize the importance of diagnosis and treatment to prevent progression to chronic ocular surface disease.

Recent scientific and clinical advances have increased our understanding of this complex group of diseases.[10] The 2007 Dry Eye Workshop (DEWS) report created a comprehensive definition for DED that is the most widely accepted version to date. The authors of the report defined DED as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface".[10] The complexity of DED is suggested by this multidimensional definition, as well as by the density of the document that summarized the body of knowledge. Other groups including the Delphi panel[11] in 2006, and a group of Canadian ophthalmologists in 2008[12] have created consensus guidelines. A comprehensive review of meibomian gland disease (MGD), a primary cause of evaporative DED, was subsequently published by the Tear Film and Ocular Surface Society in 2011.[13]

DED may be broadly classified as aqueous deficient or evaporative, although at a clinical level these categories often overlap and coexist.[10] The most severe and well-defined form of aqueous deficient DED is Sjögren syndrome (SS), a chronic autoimmune disease that preferentially attacks the lacrimal and salivary glands, as well as many other organ systems (see www.sjogrenscanada.org). The American European Consensus group for the diagnosis of SS includes a measure of aqueous production, non-anesthetized Schirmer, as a criterion for diagnosis.[14] The phenol red thread test (PRTT) can also be used to diagnose aqueous deficiency.[15] The evaporative form of the disease is often observed clinically by the breakup of the tear film, which is most typically measured invasively with the use of fluorescein.[16] Clinicians and patients would benefit from simple classification and disease staging systems.

Symptoms play an important role in the diagnosis of DED and evaluating treatment outcomes. One of the difficulties is that a patient's experience of the disease may be far more uncomfortable than it appears to a clinician when examining the clinical signs.[6] Four validated questionnaires [Ocular Surface Disease index (OSDI),[17] 5-item Dry Eye Questionnaire (DEQ-5),[18] McMonnies[19] and Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire[20]] have been shown to be useful tools to identify patients with mild symptoms that would otherwise be overlooked when simple questions about dryness are used alone; for example, in those patients who present with symptoms of intermittent blurry vision only.

There is no single objective test that leads to the diagnosis of DED. Clinicians tend to use slit lamp findings such as tear meniscus height, lid observations and corneal staining consistently in their assessments. Many other useful tests are available such as tear film osmolarity and inflammatory markers as well as conjunctival staining, but these are as yet not widely used because of the chair time and expense, and because simple and effective treatment options had not, until recently, been identified. Further, there is inconsistency among signs and symptoms, and the results of various tests for DED may not correlate with each other.[6,7] This variability among signs and symptoms can lead to confusion about the best course of treatment. For those patients who receive a diagnosis of DED and who initiate treatment, there is little guidance in the published literature to gauge treatment success.

It is with this knowledge that a group of eye care professionals gathered to create a practical clinical approach to DED. The objective of this document is to address some of the challenges associated with practical and effective screening, diagnosis and management strategies for DED in contemporary clinical practice. Further, a simplified clinical approach to categorizing the individual patient's disease into simple bins, identifying whether the disease is "episodic", "chronic" or "recalcitrant" is intended to facilitate a straightforward treatment paradigm that can be applied during most patient encounters.

SCREENING FOR DRY EYE DISEASE

Given the high prevalence and variability of symptoms, almost every adult presenting for a primary care examination should be considered to be a DED suspect until proven otherwise. The diagnosis of DED begins with a quick, selective screening. The clinician asks a few targeted questions, identifies risk factors, and conducts a brief screening examination. Patients identified with this process should be considered for a more comprehensive DED workup.

CASE HISTORY

In addition to a conventional case history, the answers to four simple questions serve as an easy and quick indicator of the likelihood of DED **(Figure 1)**.

1. Do your eyes feel uncomfortable?
2. Do you have watery eyes?
3. Does your vision fluctuate, especially in a dry environment?
4. Do you use eye drops?

If yes to any of the above questions:

1. Do you have dry mouth?

An affirmative response to any of these questions should raise the suspicion of DED and prompt a screening examination. In particular, the presence of dry eye along with dry mouth should prompt consideration for referral to another health care professional, such as a rheumatologist, for SS. Remember that ocular symptoms can occur as a result of many conditions, so be sure to rule out the myriad of other conditions that may mimic DED (**Table 1**).

RISK FACTORS

If the answers to the four screening questions suggest the possibility of DED, the presence of risk factors should be evaluated, even if the symptoms are mild. The most important risk factors associated with DED include: a history of lid, ocular, or refractive surgery; age over 40 years; female gender; use of medications known to cause DED **(Table 2)**; presence of certain systemic diseases **(Table 3)**; smoking; computer vision syndrome; and frequent exposure to harsh environments (dust, dry air, cooling and heating units, airplanes).

Table 1. *Conditions that may mimic dry eye disease.*

Allergic ocular diseases
Anterior basement membrane dystrophy
Binocular vision problems
Computer vision syndrome
Conjunctivochalasis
Contact lens/solutions induced problems
Giant papillary conjunctivitis
Infectious blepharitis
Lid issues (entropion, ectropion, lagophthalmos, floppy eyelid syndrome)
Ocular pemphigoid
Pingueculitis
Salzmann nodular degeneration
Superior limbic keratoconjunctivitis
Visual system misalignment

Table 2. *Medications with the potential to induce or exacerbate dry eye disease*[10]

Drug class	Examples	Trade Name
Antiarrhythmic drugs	Disopyramide	Norpace® and Rythmodan®
	Quinidine	BiQuin®
Antihistamines	Diphenhydramine	Benadryl®
	Hydroxyzine	Vistaril®, Atarax®
	Fexofenadine	Allegra®
	Loratadine	Claritin®
Anti-Parkinson	Benztropine	Cogentin®
	Trihexyphenidyl	Artane®
Antipsychotics	Chlorpromazine	Thorazine®, Largactil®
	Haloperidol	Haldol®
Antispasmodics	Hyoscine butylbromide	Buscopan®
	Oxybutinin	Ditropan®, Lyrinel® XL, Lenditro®
	Tolteridine	Detrol®, Detrusitol®
Tricyclic antidepressants	Amitriptyline	Elavil®
	Nortriptyline	Aventyl®, Pamelor®, Norpress®, Allegron®, Noritren®, Nortrilen®
Diuretics	Hydrochlorothiazide	Hydrodiuril®
Beta-blockers	Atenolol	Tenormin®
	Metoprolol	Lopressor®
Retinoids	Isotretinoin	Accutane®
Hormone replacement therapy	Estrogen supplements	
Selective serotonin reuptake inhibitors	Fluoxetine	Prozac®
	Fluvoxamine	Luvox®
	Paroxetine	Paxil®
	Sertraline	Zoloft®
Systemic chemotherapy	Cyclophosphamide	Cytoxan®, Procytox®
	5-fluorouracil	5-fluorouracil, 5-FU

Table 3. *Systemic diseases associated with dry eye disease*[10]

Androgen deficiency
Chronic hepatitis C
Diabetes insipidus
Diabetes mellitus
Hematopoietic stem cell transplantation
Pemphigoid
Primary biliary cirrhosis
Psoriasis
Rheumatoid arthritis
Rosacea
Scleroderma
Sjögren syndrome
Stevens-Johnson Syndrome
Systemic lupus erythematosus
Thyroid disease
Vitamin A deficiency

SCREENING EXAMINATION

The preliminary screening examination becomes necessary when a patient responds positively to any of the first four screening questions (see **Figure 1**), especially in the presence of known risk factors for DED. The screening examination is simple and is intended to be part of a regular ocular health assessment. It is based on a 3-step approach:

1. Evaluate facial symmetry, eyelids, lashes, blink, and lid closure

The practitioner should begin by looking for irregularities, crusting, redness, and other evidence of lid disease. Observe blink rate and completeness of blink, especially in patients who use computers or hand-held devices extensively.

When evaluating the lids consider the role of rosacea as many patients with this condition

have ocular manifestations.[21-24] The nose, cheeks, forehead, and chin are the most commonly affected areas. Ocular rosacea is associated with blepharitis, conjunctivitis, inflammation of the lids and meibomian glands (MG), interpalpebral conjunctival hyperemia and conjunctival telangiectasia. It is important to note that ocular signs may precede dermatological manifestations of rosacea by years; however, in the majority of cases, they develop concurrently.[21]

Four types of rosacea are recognized by the National Rosacea Society, of which two are common. Papulopustular rosacea primarily affects women in middle age (aged 30-40 years) who complain of episodic eye dryness and discomfort induced by contact lenses (CLD). These patients often have a history of flushing when exposed to triggers. External examination reveals small erythematous papules covered with pinpoint pustules. Phymatous rosacea primarily affects older men (aged >55 years) who present with thick lids, pustules, and rhinophyma.

2. Evaluate tear film: TBUT-using fluorescein strips

Instill fluid from a fluorescein strip wetted with saline onto the lower lid tarsal conjunctiva and have the patient blink normally. Do not use a fluorescein/anesthetic combination because anesthetic drops initiate reflex tearing and promote conjunctival hyperemia. Thus, evaluation of TBUT with a combination product is less valid. Observe the ocular surface with a biomicroscope and cobalt blue filter. Have the patient blink once and hold their eyes open either for as long as possible, or until until a black area is observed, indicating the break-up of the tears. Generally, a finding of < 10 seconds raises suspicion for DED.

Figure 1. *Screening for dry eye disease.*

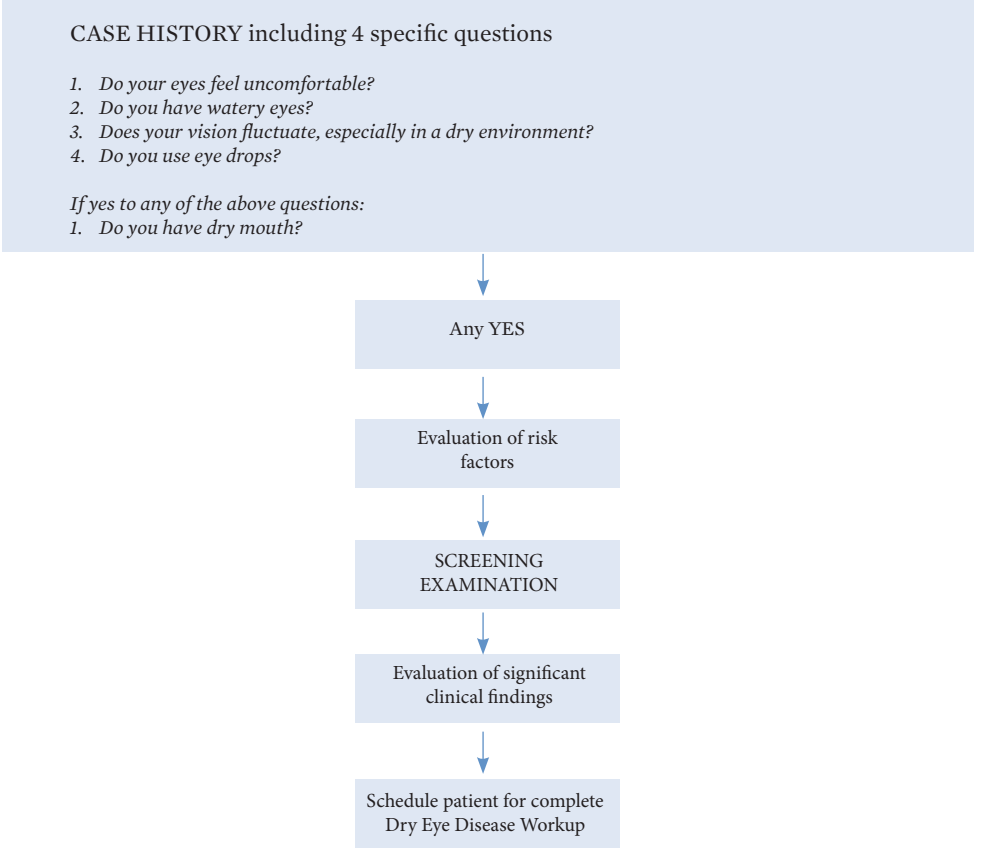


Table 4. *Criteria for Sjögren Syndrome (SS)*

Group	Criteria
American-European Consensus Group, 2002[14]	Primary SS: requires 4 of the 6 criteria, as long as either item 4 (histopathology) or 6 (serology) is positive. Secondary SS: presence of connective-tissue disease, symptoms of oral or ocular dryness, in addition of 2 of the criteria #3, #4 or #5. 1. Ocular symptoms > 3 months 2. Oral symptoms (dry mouth, swollen salivary glands or frequent use of liquids to swallow dry food) 3. Ocular signs Schirmer's test without anesthesia (<5 mm/5 min) Positive vital dye staining 4. Oral signs (histopathology): Abnormal salivary scintigraphy findings Abnormal parotid sialography findings Abnormal sialometry findings 5. Positive minor salivary gland biopsy findings 6. Positive anti-SSA or anti-SSB antibody test results
Sjögren's International Collaborative Clinical Alliance (SICCA) adopted by the American College of Rheumatology, 2009[26]	At least 2 of the 3 following findings need to be met: 1. Positive serum anti-SSA and/or anti-SSB antibodies or positive rheumatoid factor and antinuclear antibody (ANA) titer of at least 1:320 2. Ocular staining score of at least 3. 3. Presence of focal lymphocytic sialadenitis with a focus score of at least 1 focus/4 mm^2 in labial gland biopsy samples

3. Fluorescein corneal staining

After evaluating the TBUT, use the cobalt filter to observe corneal staining. Evaluate the location, pattern and severity of staining. Corneal staining associated with DED is typically evident in the lower part of the cornea, and tends to be confluent.

In summary, the presence of symptoms as revealed by the screening questions, combined with one or more signs on the screening evaluation, should prompt the clinician to proceed to a more comprehensive DED workup, either on the same or different day.

DIAGNOSIS: THE COMPLETE DRY EYE DISEASE WORKUP

Optometrists normally attempt to address all of a patient's concerns in a single primary care examination. However, the evaluation of patients with DED requires specific testing and more than an additional 5 or 10 minutes tacked on to a routine examination. Once a patient has been identified as being a DED suspect through screening, a full DED workup is recommended. This model is similar to that used by most optometrists to evaluate patients at risk for glaucoma. These patients typically return for a glaucoma workup, at which time further tests (i.e., tonometry, optic nerve head evaluation, visual field testing, pachymetry, imaging and gonioscopy) are performed. Similarly a targeted workup is required to adequately address DED.[25]

The tests described in this section comprise the comprehensive DED workup and assist the practitioner in evaluating contributing factors, such as aqueous deficiency, evaporative causes, CL wear, solution toxicity, and others. The workup should include a detailed case history including a full list of medications, with close attention to those that may contribute to ocular dryness **(Table 2)**. Careful attention to the order of testing is important to ensure that the outcome of the overall workup is not affected. As the clinician navigates through the tests, a differential diagnosis should emerge leading to an evaporative or aqueous deficient etiology, while keeping in mind that both types may coexist. The frequency of symptoms (episodic versus chronic) guides the management of the patient.

The presence of prolonged symptoms, dry mouth, low tear flow, and ocular staining prompts the clinician to consider the presence of SS. Further questioning around related symptoms is

helpful, including but not limited to, the presence of neuropathy, gastrointestinal symptoms, Raynaud syndrome and others (for more information please visit www.sjogrenscanada.org). There are two prevailing diagnostic schemes for SS, namely, the American-European Consensus Group[14] and the Sjögren's International Collaborative Clinical Alliance (SICCA) adopted by the American College of Rheumatology (2002) **(Table 4)**.[26] If SS is suspected, referral to a rheumatologist should be initiated highlighting the findings and contributory history. A solid co-management arrangement generally facilitates the most appropriate ongoing care for the patient.

Keep three key questions in mind when evaluating a patient with DED:

1. What is the frequency (episodic or chronic) and severity of symptoms and how do they affect the patient's activities (reading, driving, watching TV, etc.)?
2. What portion of the ocular dysfunction is likely attributable to evaporative causes (evaluate MG) or aqueous deficiency (evaluate quantity/volume)?
3. Is the integrity of the ocular surface compromised?

With these questions in mind, the practitioner proceeds to testing. As sequencing can affect the outcome, a specific order of testing is recommended **(Table 5)**.

EVALUATION OF SYMPTOMS

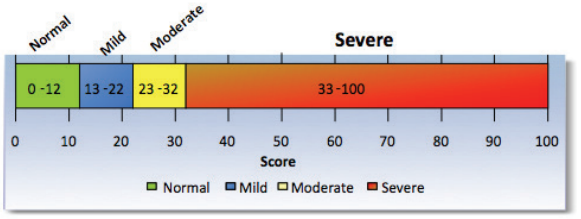
DED is largely a symptomatic disease.[27,28] As such, clinicians need validated tools to evaluate symptoms and appreciate how the daily lives of patients are affected. It is important to start the DED work-up with an assessment of symptoms, prior to instilling any drops or manipulating the eyes, in order to minimize the effect on the results.

Table 5. *Suggested order of dry eye disease work-up*

1.	Case history with dry eye questionnaire
2.	Osmolarity (if available)
3.	Tear quantity and volume Schirmer 1 (no anesthesia) or Phenol red thread test (PRTT)/Cotton thread test (CTT)
4.	Anterior segment evaluation with white light (focus on the lid margin)
5.	Tear break-up time (TBUT)
6.	Ocular surface integrity (using ophthalmic dyes and appropriate filters) Cornea Conjunctiva
7.	Meibomian gland (MG) expression and assessment
8.	Adjunctive tests *

**order of testing may vary as a result*

Figure 2. *Ocular Surface Disease Index (OSDI) severity scale.*



The Ocular Surface Disease Index (OSDI) [29] is a self-administered 12-question assessment of symptoms and how they affect vision-related tasks (i.e. reading, driving, computer use, etc.).[17] The questionnaire is divided into three sections: the first evaluates the frequency of symptoms; the second evaluates the effect of symptoms on daily tasks; and the third evaluates the effect of environmental factors, such as windy conditions and air conditioning. The scores on the three sections are summed to arrive at a final OSDI score, which ranges from 0 to 100, with higher values indicating greater symptom severity [normal (<12), mild (13-22) moderate (23-32) or severe (33-100), **Figure 2**]. The OSDI has a high degree of sensitivity (80%) and specificity (79%) for discriminating patients with and without DED, and is even better at identifying patients with severe disease (sensitivity 87%; specificity 96%).[17]

The OSDI is available in English and French, although only the English version has been validated. The French version has been professionally translated but not validated.[29]

The validated McMonnies questionnaire can be integrated into practice easily.[19, 30-32] Responses to questions about gender, age, medication use, general health and contact lens (CL) wear increase the suspicion for dryness and prompt the practitioner to perform further tests. Each response is assigned a numeric value and the sum is then compared to a risk table. The higher the total score, the greater the risk of dryness. The cut-off point for DED is 14.5 out of a possible 45.[33, 34] The questionnaire has a high sensitivity (98%) and specificity (97%) for DED, but is not as sensitive in categorizing marginal DED.

The DEQ-5 is a user-friendly questionnaire that is quick and easy to complete.[18] The patient rates the frequency (never, rarely, sometimes, frequent, and constant) with which they have experienced three symptoms (watery eyes, discomfort and dryness) in a typical month. The patient is also asked to rate the increase in intensity of discomfort and dryness throughout the day. Each response corresponds to a numeric value that is used to calculate a final DEQ-5 score. A DEQ-5 score >6 is indicative of DED and a score >12 is indicative of SS.

The SPEED questionnaire involves a series of four key DED symptoms that are rated on frequency and severity combined with 3 additional questions on artificial tear use, blepharitis and frequency of fluctuating vision.[20] The SPEED score is the sum of the Symptom and Frequency Scores, which range from 0 and 32. No cut-off value for DED has been adopted to date.[20]

Although several other validated DED questionnaires are available, some [DEQ, Impact of Dry Eye on Everyday Life (IDEEL)] are more suitable for research and will not be discussed here.[35, 36]

TEAR OSMOLARITY

Tear osmolarity analysis is a point-of-care test that provides immediate results. A small sample of tears is obtained at the temporal edge of the tear meniscus with a TearLab pen. Once a 50 nL sample is obtained, the device beeps and a light indicates that the collection is complete. The pen is then placed into the reader and within 10 seconds the analysis is complete and the result is displayed in mOsmol/L.

Tear film osmolarity is the most accurate single test for DED,[8, 9] but should not be used in isolation for the diagnosis of DED. Generally readings higher than 308 mOsmol/L are considered diagnostic of DED. Higher values and a variance of >8 mOsmol/L between eyes indicate more severe disease.[8, 9]

EVALUATION OF TEAR FLOW

DEWS categorized DED as being primarily aqueous deficient or evaporative in origin.[10] Although the latter is more common, tear flow must be quantified to distinguish between these two categories. Measuring tear flow can assist in the initial diagnosis of DED and can be used to determine and monitor treatment options. Two readily available tests, the Schirmer test and the PRTT/CTT are useful in this regard.

Figure 3. *Phenol red thread test (PRTT)/Cotton thread test (CTT) placed in lower lid to measure residual tears.*

The Schirmer test has a reputation for causing discomfort, but is a sensitive test for detecting tear deficiency, particularly when SS is suspected.[37-40] When performed without anesthesia (Schirmer 1), the test measures the quantity of residual tears accumulating in the lower cul-de-sac during a 5 minute period. A value >10 mm/5 min is considered to be normal **(Table 6)**. Lower values indicate increasing degrees of tear deficiency. Care must be taken to avoid stimulating reflex tearing, which renders the result inconclusive for most cases of DED. The test is more robust in tear-deficient DED, in which the patient is incapable of producing adequate tears.[7] The sensitivity (85%) and specificity (83%) of the Schirmer test are relatively high for differentiating between normal individuals and those with tear deficiency.[41]

The PRTT is a fast and more comfortable alternative test for assessing tear volume. It is performed by inserting a phenol red-impregnated cotton thread in the lower fornix of the lid for 15 seconds **(Figure 3)**.[42-45] The change in colour of the wetted thread is easy to observe and measure directly with the scale on the package. A value >9 mm/15 sec is considered to be normal **(Table 6)**. The sensitivity (86%) and specificity (83%) are comparable to that of the Schirmer test (see above).[15] As with any measure of tear quantity, the clinician needs to be aware of high readings as these may be suggestive of reflex tearing.

There are more sophisticated ways of quantifying the lower tear meniscus height (TMH) as an indirect measure of tear volume (e.g., anterior optical coherence tomography (OCT) or corneal topography). Although these tests are generally not available to most clinicians, they are gaining acceptance.[46-50]

Figure 4. *Mastrota paddle used to express the meibomian glands.*

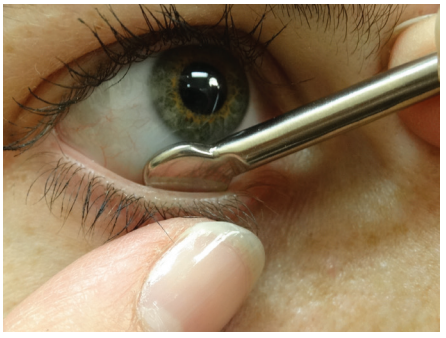


Figure 5. *Meibomian Gland Evaluator (TearScience) used to express the meibomian glands with a consistent force.*

ANTERIOR SEGMENT EVALUATION

A systematic assessment of the lashes, lid margin, cornea, and bulbar and palpebral conjunctiva is needed to assess the proper functioning of the tear film and ocular surface.

Particular attention is given to the lid margin where evidence of blepharitis (anterior or posterior), lash loss (madarosis), thickening of the lid margin (tylosis), lid inapposition, notching of the lid margin, posterior migration of gland orifices, and dilation of small blood vessels along the lid margin (telangiectasia) can be observed. Debris accumulated on the lashes, whether from make-up, environmental contaminants or from anterior blepharitis, can fall onto the tear film, increasing the viscosity and slowing the movement of the tear film towards the punctum.

EVALUATION OF MEIBOMIAN GLANDS

Expressing the MG and evaluating the composition of their secretions is important.[51] Assessing the MG can provide insight into the factors contributing to evaporative DED. The appearance and consistency of meibum expressed by the Mastrota paddle, the Meibomian Gland Evaluator or simply by a finger or cotton swab, can be described in terms that correspond to increasing levels of MGD (clear, cloudy, cloudy with debris, thick or paste-like, or non-expressive).[51] Saponification, or the appearance of bubbles similar to a soap foam (frothing) along the lid margin, can indicate hypersecretion of the MG.[52] The foam often accumulates in the temporal canthus and is easily observed using a slit lamp.

Tools such as the Mastrota paddle[54-56] and the Meibomian Gland Evaluator (TearScience)[55, 56] have been developed to assist in MG expression, although using the thumb to press on the lid or a wet cotton swab behind the eyelid are effective alternatives.

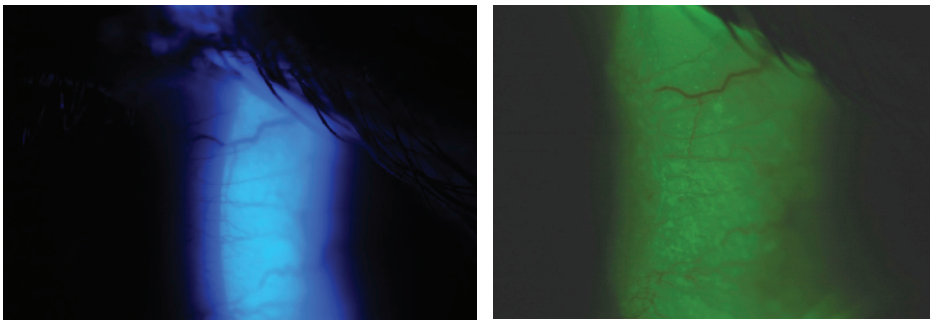
The Mastrota paddle (available from Ocusoft) is a 7 cm titanium instrument with rounded edges that is placed behind the lower lid to assist in the expression of the MG **(Figure 4)**. Using a finger or thumb, gentle pressure is applied to the lower central to nasal lid to express the MG against the surface of the paddle.

The Meibomian Gland Evaluator looks like a USB key **(Figure 5)**. The white tip is pressed tangentially against the central lower lid to exert pressure equivalent to that of a normal blink (i.e.. between 0.8 and 1.2 g/mm^2) and then is retracted into the blue housing.[57]

EVALUATION OF OCULAR SURFACE INTEGRITY

The evaluation of the integrity of the ocular surface, cornea and conjunctiva is an essential part of the DED workup. Fluorescein is best suited for assessing the cornea, while lissamine green (LG) is preferred for the conjunctiva.[58, 59] The use of both ophthalmic dyes is optimal to ensure adequate evaluation of ocular surface integrity. LG has a robust safety profile,[60] and is better tolerated than rose bengal, which stings on instillation;[61] however, obtaining LG is a challenge in Canada and the U.S.

Figure 6. *Conjunctival tissue observed under cobalt blue illumination (left) and enhanced with a yellow barrier filter (right).*



Staining of the cornea and conjunctiva indicates that the integrity of the tissue has been compromised and that inflammatory mediators are present.[10, 62] Many factors can cause corneal staining including prolonged surface exposure due to infrequent or incomplete blinking,[63, 64] toxic effects of preservatives in eye drops,[65, 66] CL wear and exposure to CL care solutions,[67-70] and lid margin inflammation caused by blepharitis. A thorough case history that includes systemic and ocular medication use, and the type of CL and cleaning solutions used, will tease out some of the factors responsible for the breakdown in ocular surface integrity. Whatever the cause, or the ophthalmic dye used, proper documentation of staining should include the pattern, position, depth and the grade (identifying the scale that is used).[71]

Overall, corneal staining in non-CL wearers occurs more frequently in the inferior quadrant, with the central cornea being affected least.[72] When adding fluorescein it is important to control the instilled volume. If the strip delivers too much dye, quenching can occur and it may be difficult to see any pattern until the excess is cleared from the eye. Controlling the volume (by shaking off the excess prior to instillation) and having the patient blink several times to distribute the fluorescein should optimize the assessment.[73] Adding a yellow barrier filter enhances subtle staining and is essential to use to assess conjunctival fluorescein staining **(Figure 6)**. Most new biomicroscopes have an integrated barrier filter. Otherwise, a hand held filter may be used.

Identifying the pattern and location of staining provides clues to the cause of the symptoms. Staining may occur as scattered superficial dots (punctate staining), or coalesce to form patchy or confluent areas. These patterns may be located in any quadrant of the cornea (superior, inferior, temporal or nasal) or may even be interpalpebral. Staining in the superior quadrant is indicative of superior limbic keratoconjunctivitis (SLK), a condition found mostly in women aged 20-60 that is believed to be related to a tight lid/globe interface or thyroid disease. Diffuse punctate staining across the cornea may be indicative of toxicity. Reviewing the preservatives in eye drops or CL care solutions may reveal the cause of the observed fluorescein hyperfluorescence, which

Figure 7. *Distinguishing the difference between solution-induced corneal staining (SICS) (on the left), and DED staining (on the right)*

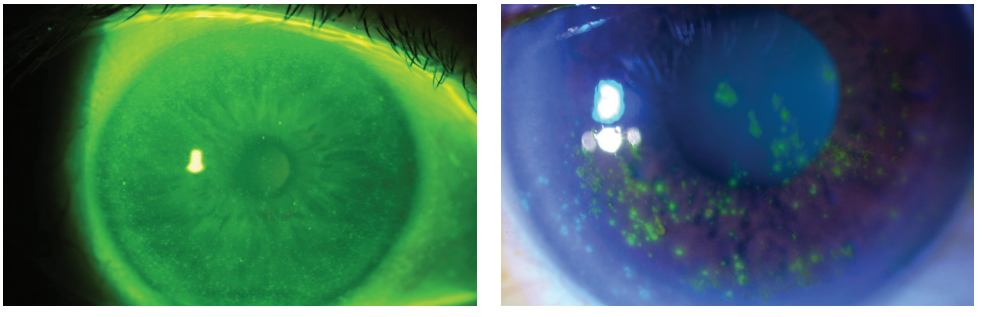


Figure 8. *Lid wiper epitheliopathy (LWE) observed below the meibomian gland openings in the upper everted eyelid of patient's left eye.*

is known as solution-induced corneal staining (SICS) and should not be confused with diffuse superficial punctate keratitis (SPK) **(Figure 7)**. SICS is not considered to be true staining but, rather, is associated with increased permeability of epithelial cell membranes after exposure to preservatives. It is not associated with a higher infection rate. The presence of the transitory SICS in soft CL wearers should prompt the clinician to review the compatibility of the CL and the solutions.[67] It is highly recommended to consider a refit into daily disposables at that time.

Corneal staining near the lid margin (superior or inferior) points to blepharitis. Careful assessment of the lashes and lid margins is essential to determine the source of this staining pattern. Staining between the lid margins (interpalpebral) points to an incomplete or ineffective blink, or to nocturnal lagophthalmos, conditions that leave the cornea exposed to dehydration. Sectoral staining may be caused by a foreign body or a localized irritant, such as GPC, concretions, a loose lash or debris.

Conjunctival bulbar staining also provides insight into the etiology of DED. Both fluorescein and LG can be used to assess the conjunctiva, although LG is more sensitive, especially for symptomatic CL wearers.[59] Staining occurs more frequently on the nasal conjunctiva in patients with DED, whereas temporal staining is more indicative of SS.[74] These new clinical findings reinforce the use of ophthalmic dyes in a comprehensive DED workup in assessing the integrity of both the cornea and conjunctiva.

Some practitioners advocate simultaneous double staining of the ocular surface with both fluorescein and LG as a way to save chair time. Double staining correlates well with symptoms and tear film stability in patients with DED. Typically, the nasal conjunctiva stains to a greater extent than the temporal conjunctiva, with the cornea being affected less. To date, there are no commercially available combination dyes in Canada.

The clinician's attention should also be directed to the inner lid margin, above the Marx line, to an area called the "lid wiper". The lid wiper is that part of the inner upper palpebral conjunctiva that is in contact with the cornea during a blink.[76] This area stains with both fluorescein and LG, and lid wiper epitheliopathy (LWE), or upper lid margin staining (ULMS), as it is also termed,[77] may be present in symptomatic patients, more often in CL wearers,[78] despite a normal TBUT **(Figure 8)**. The presence and intensity of the LWE may be related to decreased mucin production, more specifically mucin-5AC, in symptomatic CL wearers.[79, 80]

To view LWE, the upper lid is everted to expose the area under the opening of the MG. It has been suggested that instilling dye from two strips of LG 1 minute apart then waiting for at least 3 minutes optimizes the viewing of LWE.[81] LWE can be graded, and its progress monitored, by measuring the thickness and length (in mm) of the stained area.

EVALUATION OF TEAR FILM STABILITY

Once fluorescein has been instilled to evaluate tissue integrity, the stability of the tear film can also be assessed. The tear break-up time (TBUT), probably the most familiar test for this

purpose, is defined as the time (in seconds) needed for the first break or rupture in the tear film after a blink. Despite its long history of use, the results are often highly variable and many practitioners have lost confidence in the test. However, the variability can be reduced by adhering to a standardized method, which includes wetting the fluorescein strip with sterile saline, controlling the volume instilled (by shaking off excess), tapping the lower tarsal conjunctival surface (as opposed to bulbar) and delivering only a small volume.[73, 82] The clinical value of the TBUT can be further improved by calculating the average of two consecutive measurements.[7]

A TBUT of more than 10 seconds is indicative of a stable tear film. In contrast, patients with DED tend to have a rapid TBUT, typically <5 seconds. Ethnic differences exist, mainly due to differing lid morphologies, such as those in Asian patients, in whom the TBUT is often shorter.[83, 84]

Fluorescein can reduce tear film stability,[85] and less invasive methods are available for the measurement of TBUT. The non-invasive break-up time (NIBUT) can be measured by using the reflected mires of a corneal topographer or other instrument. These methods generally yield longer break-up times.[86-89]

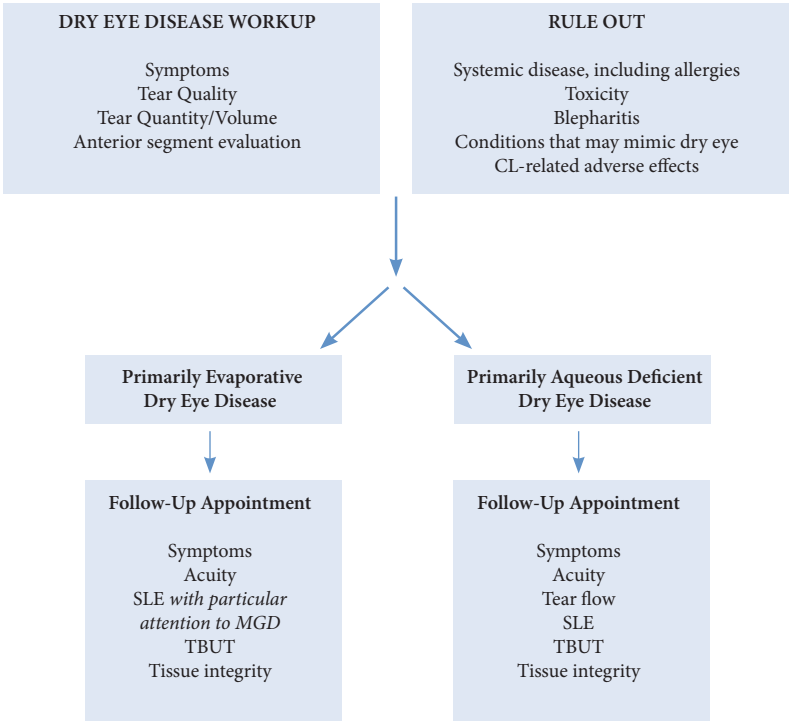
Normal values expected in a comprehensive DED workup are summarized in **Table 6**. Additional tests can be performed, depending on the case, the availability of equipment and the expected clinical value. A description of adjunctive tests and some emerging technologies is provided in the **Supplementary Appendix.**

Table 6. *Normal values for dry eye disease testing*

Evaluation	Test	Normal values
Symptom questionnaire	OSDI	<12 /100
	McMonnies	<14.5/45
	DEQ-5	<6 for dry eye
Tear volume	Schirmer	>10 mm/5 min
	PRTT	>9 mm/15 sec
Tear osmolarity	TearLab Osmometer	<308 mOsml/L
Anterior segment evaluation	Slit Lamp examination	
Tear film	Viscosity	Medium-fast
	Debris	Little to none
Lashes	Lashes	No debris, collarettes or dandruff cuff
Meibomian glands	Expression	Easy
	Secretions	Clear, liquid
Lid margin	Lid margin	Good apposition, smooth
Tear film stability	FL-TBUT	>10 sec
	NIBUT	> FL-TBUT
Tissue integrity (using ophthalmic dyes)	Cornea Conjunctiva	No staining to trace staining (<grade 2)

Figure 9 summarizes the recommendations in this section to help guide the clinician in the management of dry eye disease patients.

Figure 9. *Summary of Full DED workup.*



GENERAL PRINCIPLES OF MANAGEMENT: OVERVIEW AND CLASSIFICATION

A practical, clinician-friendly approach is proposed whereby patients with DED are categorized as having "episodic" or "chronic" disease at their initial visit. A third category, "recalcitrant", is reserved for patients who do not respond sufficiently to the available battery of treatment options and, therefore, require more intensive therapies including systemic medications or surgery. **(Table 7)**

The overarching principle in the management of patients with DED is to reduce symptoms and return the tear film and the ocular surface to as close as possible to a normal state of health. While this may be achieved in patients with episodic or mild disease, it is more challenging in patients with chronic DED, in whom moderate or severe symptoms and signs are more common.

Episodic disease occurs when symptoms and signs are not consistently noted; that is, they are present only under certain environmental conditions or during specific visual tasks. Patients with episodic disease may report varying levels of symptom severity, but experience symptoms only when situations such as reduced blinking, CL wear or environmental conditions overwhelm the stability of the tear film or homeostasis of the ocular surface. Episodic disease may result from tear flow deficiencies and/or tear evaporation, but in either case the effects are transient.

DED that is not episodic must be, by definition, **chronic** in nature. The unifying mechanism

in chronic DED is presumed to be consistent inflammation. Chronic DED is also influenced by environmental conditions, and symptoms and signs continue to vary in severity. While the recommended therapies for episodic disease are used concurrently, the focus in chronic DED is on controlling the inflammatory mediators to reduce symptoms and signs, and to minimize disease progression.

Recalcitrant DED applies to those patients in whom primary interventions have proved to be insufficient and in whom additional and/or uncommon ("rescue") strategies may be required. This may occur when, despite maximal application of conventional therapies, a patient remains symptomatic, or the effects to vision and/or tissue damage on the ocular surface progresses to the point where the risk of more serious sequelae is significant. These uncommon interventions may include unique devices (e.g. scleral lenses, amniotic membranes), specialized medications (e.g. autologous serum eye drops, secretagogues), or surgery (e.g. tarsorrhaphy), that are not normally available to the primary eye care practitioner.

TREATMENT FOR EPISODIC DISEASE

The management strategies for episodic DED target the presenting symptoms, and attempt to control the exacerbating external conditions. The history and diagnostic workup will often reveal early stages of disease, and management is focused on removing or limiting the environmental cause. The practitioner is advised to use the most appropriate treatment, and to educate each patient not only about the treatment, but also about the rationale for its application.

MANAGEMENT OF DRY EYE DISEASE

Table 7. *A novel clinical classification and management strategies in DED*

TYPE	MANAGEMENT	
EPISODIC	Tear supplements / lubricants	*Consider composition of available agents (lipid-based, products that restore the mucin layer, overall)*
	Ocular	*Hot compresses, lid hygiene, moisture chamber glasses, modifications to CL wear (switch to daily disposables)*
	Non-ocular considerations	*Environmental (ambient humidity, air movement, computer use), systemic medications and supplements, alcohol, smoking, hormonal status, sleep apnea*
CHRONIC		**Episodic management +**
	Short-term	*Topical corticosteroid*
	Long-term	*Topical cyclosporine* *Essential fatty acids*
	Supportive	*Oral tetracycline / macrolide, lacrimal occlusion, meibomian gland (MG) expression (in-office), sleep masks/lid taping*
RECALCITRANT	Ocular	*Scleral lenses, filament removal, autologous serum eye drops, amniotic membranes, tarsorrhaphy, other surgical techniques*
	Systemic	*Secretagogue, systemic immunosuppressive therapies*

TEAR SUPPLEMENTATION

Tear supplements or lubricants are the mainstay of treatment across the full spectrum of DED. There is evidence to show that the use of tear supplements is beneficial to the ocular surface. For example, ocular surface staining with rose bengal improves by 25-33% within one month of using tears, gels or hyaluronate-based supplements.[90] There are many different active ingredients and formulations of tear supplements, the most relevant of which are described in **Table 8**. Evidence and clinical wisdom will guide the clinician as to the product and frequency of use to recommend for a given patient. However, the use of ocular lubricants more than 4 times a day should prompt the clinician to recommend a non-preserved product to reduce the

risk of toxic adverse effects on the ocular surface. Preservative-free products should also be favored in the presence of other ocular topical medications.

Tear supplements lubricate, can promote ocular surface cell health and may alter the inflammatory state of the ocular surface. They do so indirectly by affecting the tear film osmolarity and, possibly, by decreasing the concentration of inflammatory mediators in the tear film, but do not specifically target the underlying inflammatory disease associated with chronic DED. Because of this, tear supplements are valuable adjunctive therapies when using anti-inflammatory therapies to treat DED. Properties of tear supplements that are important for relieving symptoms and promoting ocular surface healing include: osmolarity, the presence of and type of preservative, inclusion of polymers to increase retention time, and lipid composition **(Table 8)**.[90-92]

Table 8. *Considerations when selecting a tear supplement for a patient with dry eye disease*

Property	Consideration for Tear Supplements	Recommended examples
Osmolarity	Should ideally shift tear osmolarity from a hyperosmolar to an isotonic state over time	Blink®, HYLO®, Hypotears®, Refresh Optive Advanced®, Theratears®
Preservatives (multidose formulations)	If preserved products are to be used, avoid benzalkonium chloride (BAK) and choose those that contain Polyquad, Purite or sodium perborate	Genteal®, Refresh® (Purite) Tears Naturale II® (Polyquad), Theratears® (sodium perborate)
Preservative-free (most are unit-dose)	Preservative-free products are preferred, especially as frequency of use increases or in the presence of other topical medications	Bion Tears®, HYLO, HYLO-gel® I-Drop®, I-Drop® PM, I-Drop® Pur Gel®, Refresh Celluvisc®, Refresh Endura®, Refresh Optive Advanced® Sensitive, Refresh Plus®, Systane® Ultra PF, Tears Natural Free®, Theratears® PF
Polymers and viscosity	Enhance hydration of the mucin-gel of the tear film and increase retention time of tear supplements Consider use of low viscosity products (drops, gels) during the day and more viscous products (ointments) during the night	Carboxymethylcellulose, sodium hyaluronate, hydroxypropyl guar-borate
Lipid Content	Oil-based emulsions restore the inadequate lipid layer in patients with MGD and DED	Liposic®, Refresh Endura®, Refresh Optive Advanced®, Refresh Ultra®, Systane® Balance
Sodium hyaluronate-containing products	For LWE issues	Blink®, Hyabak®, HYLO®, I-Drop®

OCULAR CONSIDERATIONS

A number of simple measures can be recommended to relieve the symptoms and signs of DED. These include hot compresses, lid hygiene (when indicated), moisture chamber spectacles and modification of existing CL wear.

Hot Compresses

Hot compresses are a mainstay of the management of DED associated with MGD. The melting point of the lipid secretions of patients with MGD is elevated compared to those of patients without MGD (from 32 to 35 °C). Tear film lipid layer thickness increased by more than 80% in patients with obstructive MGD after application of a 40 °C compress for at least 4 minutes, and improved by a further 20% after 15 minutes of treatment.[93] While hot compresses are often recommended and may improve secretion from accessory tear glands, their method of use is not standardized. Usually, it is recommended that hot compresses be used on a daily basis for a few weeks or months then, to establish a maintenance regimen, 2 to 3 times a week, depending on the degree of improvement in the condition. Unfortunately, effective use of hot compresses is time intensive and patients find it difficult to maintain a consistent daily regimen

with traditional methods such as a face cloth.[94] Alternate products such as MGDRx EyeBag , Bausch & Lomb Thera Pearl® , Thermoeyes goggles and the Bruder Eye Hydrating Compress are effective devices that help patients adhere to a regimen. Lipiflow® is an expensive in-office treatment that can be recommended for recalcitrant or non-compliant patients, but also as a primary therapy.

Lid Hygiene

Lid hygiene is generally recommended for patients with anterior blepharitis, and despite the number of products available (i.e., TheraLid™, Systane™ Lid wipes, and I-Lid n' Lash®), procedures for use have not been standardized. It is important that patients understand how to gently cleanse their lids and lashes and how to prevent the product from contacting and irritating the ocular surface. Products used for lid hygiene contain many components, some of which may not be listed on the label. Recently, products with tea tree oil have been recommended for blepharitis related to *Demodex folliculorum* (a parasitic mite). For example, shampoos, facial hygiene products, lid wipes (i.e. Cliradex) and solutions are being formulated in higher concentrations for in-office treatment of *Demodex* lid infestations..

Moisture Chamber Spectacles

Moisture chamber spectacles are a highly effective but underutilized option for increasing ambient humidity and minimizing the impact of environmental conditions on the ocular surface. Patients often start by wearing a pair of sunglasses to reduce symptoms in outdoor environments. If this is effective, they should be encouraged to use clear moisture chamber glasses indoors and outdoors in low light situations. A number of brands are available that allow for the incorporation of patients' prescriptions; however, a good fit is critical to achieving comfort and success.

NONOCULAR CONSIDERATIONS

There are a host of non-ocular factors that contribute in varying degrees to the symptoms and signs of DED. Although many of these factors are non-modifiable, they are worth considering in order to educate patients on the role they play in the disease.

Ambient humidity, air movement and the use of computers and hand-held devices, are all important factors in DED. Maintenance of high ambient humidity is a critical step in the environmental modifications that can help patients to cope with tear evaporation. The use of small humidifiers in the office or home can improve symptoms dramatically. This strategy is especially useful in climates where air conditioning or heating are used for extended periods. Air movement by fans or wind is harmful to the fragile tear film and ocular surface, and could be protected against with moisture chamber goggles, or at the very least, by spectacles. Airplane and car travel are particularly bothersome and damaging. Ocular allergies may cause or exacerbate DED and use of oral antihistamines may further dry the tear film and worsen symptoms.[95]

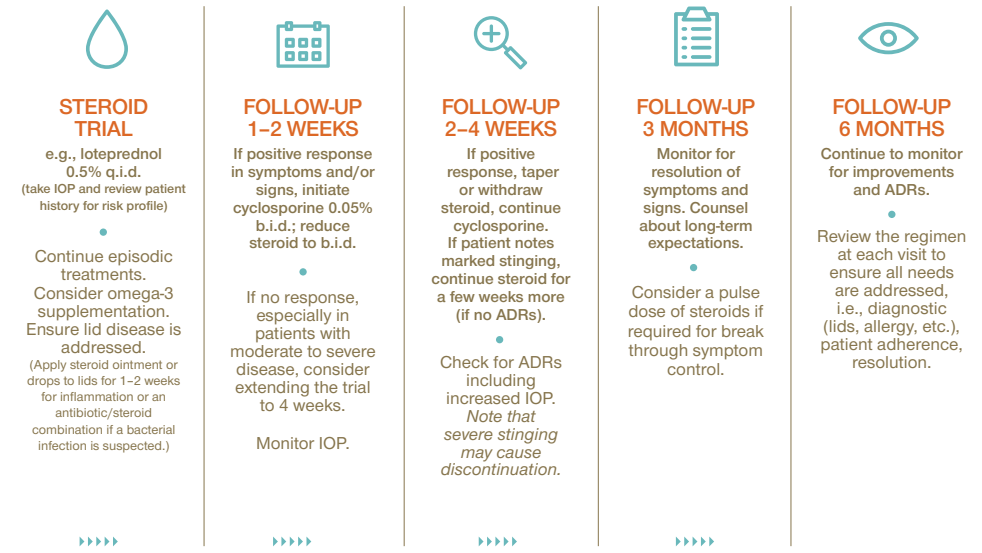
A large number of systemic medications have drying effects on the mucous membranes of the eyes (e.g. antihistamines, anti-depressants, diuretics **[Table 2]**). While these can be discussed with the patient and prescriber, essential medications will not normally be discontinued due to DED. Consumption of alcohol and exposure to cigarette smoke are environmental triggers that should be avoided.

Androgen/estrogen imbalance contributes to DED. Women are more affected than men. While clinical trials of both androgen and estrogen eye drops are ongoing, some patients may benefit from topical hormone therapies.[91]

Continuous positive airway pressure (CPAP) for sleep apnea may exacerbate morning DED symptoms due to forced air escaping from poorly fitting masks. A flexible shield (Quartz) has been developed to protect the eyes while not affecting the fit of the CPAP mask.

The use of computers and hand-held devices is associated with episodic symptoms and exacerbations of chronic DED. It is important to evaluate time spent on these devices, blink

Figure 10. *Management of chronic dry eye disease.*



rate and completeness, and the role of CL wear. Computer workstations should be modified to ensure that screens are placed below the primary line of sight in order to minimize lid aperture width and subsequent tear evaporation.

MANAGEMENT OF CHRONIC DISEASE

Even with the diligent use of conventional (episodic) treatments (e.g. tear supplements, hot compresses), many patients with DED experience progression of symptoms and/or ocular surface signs. This is due, at least in part, to ageing, as all measures of tear function decline with age;[96] however, the lack of targeted anti-inflammatory therapy, poor adherence and underlying chronic systemic diseases may also contribute to progression.

An abundance of research in the last decade has prompted a shift in thinking about DED. A self-perpetuating cycle is occurring on the ocular surface, whereby abnormal tear secretion alters the tear film composition and, in turn, increases tear film osmolarity. Increased tear film osmolarity stimulates the production of inflammatory mediators on the ocular surface, which causes the malfunction or destruction of cells that secrete various components of the tears.[10]

As inflammation is the core mechanism responsible for chronic DED regardless of the cause, strategies aimed at arresting the cycle of inflammation are pivotal in healing the ocular surface, reducing symptoms and minimizing disease progression.[97]Anti-inflammatory treatment involves a trial of a topical corticosteroid, which, if tolerated and successful, is followed by long-term immunomodulatory therapy. Regardless of the episodic treatment recommendations, anti-inflammatory therapy is at the forefront of the treatment paradigm for chronic disease. Breaking the cycle of inflammation early in the course of the disease may prevent the need for more substantial interventions as the patient ages.

SHORT-TERM ANTI-INFLAMMATORY TREATMENT

Corticosteroids

Corticosteroids are effective in relieving the symptoms and signs of chronic DED.[62, 98-100] As soon as the patient's condition is identified as anything but episodic, a steroid trial should be initiated (subject to the usual cautions and contraindications). Not only are corticosteroids helpful to gauge the efficacy of anti-inflammatory therapy in an individual patient, but they are also used to ease a patient into long-term anti-inflammatory treatment options, primarily topical cyclosporine **(Figure 10)**.

Specific signs and symptoms that might prompt the use of corticosteroids include ocular surface discomfort, obvious inflammation of the lids and ocular surface, corneal staining, low tear production, and inadequate relief of symptoms with hot compress and tear supplements. It is imperative to consider corticosteroid therapy when the conjunctiva and cornea show consistent signs of ocular dryness (e.g., by fluorescein or LG staining). However, long-term use is limited due to adverse effects such as cataracts, immunosuppression, and the potential for increased intraocular pressure (IOP).[101]

While many topical corticosteroids have been evaluated and are effective,[62] the most obvious one to consider is loteprednol etabonate 0.5% (Lotemax®), due to its similar efficacy, and superior safety profile compared to the most potent ketone-based topical corticosteroids.[102] Loteprednol is less likely to cause an IOP spike, cataracts or delayed tissue healing than other similarly effective steroids.[98, 99]

If a patient is unable to tolerate loteprednol, a preservative-free formulation should be considered. Methylprednisolone acetate 1% has shown favourable results in DED associated with SS, with all patients experiencing improvement in symptoms and signs within 8 weeks when used up to four times per day. Of note, improvement (measured by impression cytology) lasted an average of 56.6 weeks after a first pulse, and even longer after a second.[103] This type of non-site-specific steroid has the potential to cause a significant increase in IOP and steroid-induced glaucoma, cataracts, as well as other adverse effects. For these reasons, these agents are generally reserved for patients in whom loteprednol cannot be used. Regardless of the corticosteroid product that is prescribed, the clinician should establish an appropriate follow-up schedule for each patient.

Generally, when inflammation is considered to be present in DED, loteprednol 0.5% is administered q.i.d and continued for 2 to 4 weeks, or sometimes longer, during which time efficacy, IOP and side effects are evaluated. If symptoms or signs improve, then treatment with cyclosporine 0.05% (Restasis®) may be initiated. Barring any complications, the corticosteroid is continued concurrently at a reduced frequency with the cyclosporine for another 2 to 4 weeks to mitigate the transition to monotherapy with cyclosporine **(Figure 10)**.

If inflammation of the lids is apparent, application of a topical corticosteroid ointment such as dexamethasone 0.1%, or loteprednol 0.5% is appropriate and may precede use of loteprednol drops. Alternatively, use of an antibiotic-steroid combination product may be considered (e.g., tobramycin 0.3%/dexamethasone 0.1% (Tobradex®), neomycin 0.35%/polymyxin B/dexamethasone (Maxitrol®).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have a limited role in the management of DED. Their main use is to reduce or eliminate the pain and abnormal membrane-bound mucin layer associated with filamentary keratitis.[104, 105]However, this may also be accomplished with corticosteroids. Topical NSAIDs, especially generic versions, must be used with caution as corneal melting has been associated with chronic use after surgery and in patients with uncontrolled autoimmune disease.[106]

LONG-TERM ANTI-INFLAMMATORY TREATMENT

Topical cyclosporine

Topical ophthalmic cyclosporine 0.05% (Restasis®) formulated with castor oil as an emulsion vehicle is an effective and safe treatment for chronic inflammation on the ocular surface. Cyclosporine modulates T-cell-mediated inflammation and, although some patients may report symptomatic improvement in as little as a couple of weeks, it may take 3 months or longer to show a demonstrable effect in symptoms or signs.

The use of this drug is evolving. The original approval for topical cyclosporine was based on an increase in tear flow. Treatment with topical cyclosporine is commonly used in moderate to severe DED but it has been shown to prevent progression in patients with milder forms of

DED.[97] Cyclosporine is also useful for the long-term treatment of MGD.[107] Indeed, long-term treatment with cyclosporine outperformed a combination of tobramycin/dexamethasone in patients with posterior blepharitis.[108]

Before initiating treatment with cyclosporine, it is important to discuss the course of the treatment in order to manage patient expectations. While improvement in signs and symptoms can be seen within the first 8-12 weeks of treatment, patients with severe chronic or recalcitrant disease can take up to a full year to experience improvement. It is important to use the treatment long enough to evaluate the condition properly and to encourage adherence at follow-up visits. Photodocumentation can help a patient to understand small and subtle changes in their ocular condition, and is helpful to increase treatment adherence. Clinical positive outcomes can be noted earlier if an anti-inflammatory treatment is instituted before application of cyclosporine.

The main adverse effect noted with cyclosporine is burning on instillation, which was experienced by 17% of subjects in a clinical trial (10% higher than that associated vehicle alone).[109] Cyclosporine is not associated with steroid-induced ocular adverse effects, and given the need for long-term therapy in chronic DED, the long-term safety profile is one of the key benefits of cyclosporine.[110]

Essential fatty acids

The role of essential fatty acid (EFA) supplementation in the treatment of DED is evolving. However, clinical recommendations vary because the most effective form of EFA and the optimal dosing regimen is yet to be determined.

EFAs, such as omega-3 fatty acids, are essential nutrients that must be acquired in the diet. They include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are found in cold-water fish such as mackerel, anchovies, sardines, albacore tuna, and salmon, and alpha-linolenic acid (ALA), which is found in plant sources such as flaxseed, for example, but must be converted to EPA and DHA to be used by the human body.

Gamma-linolenic acid (GLA) is an omega-6 EFA with anti-inflammatory properties that is found in black currant seed oil, evening primrose oil and to a lesser extent borage oil. GLA must be combined with EPA/DHA at a minimum ratio of 1:1, otherwise there is a risk that it will have proinflammatory effects. In the presence of EPA/DHA, GLA has been shown to have significant anti-inflammatory properties and to be effective in DED with an inflammatory component.[111, 112] GLA has been shown to be useful in the management of CL-associated DED,[113] KCS associated with SS,[114] and post refractive surgery DED.[115] Moreover, GLA has been shown to improve signs and symptoms of moderate to severe KCS with inflammatory components,[116, 117] and DED associated with MGD.[118]

While the best form and optimum dose of EFA continues to be debated, it is clear that these compounds have anti-inflammatory effects, and are helpful for the treatment of DED.[119-121]

ADJUNCTIVE TREATMENTS

In addition to corticosteroids and topical cyclosporine, a number of other treatments with anti-inflammatory properties are available for the treatment of DED, but are not recommended in all patients. Those listed in this section are indicated when certain lid diseases, specifically MGD with or without rosacea, are a significant component of DED.

Oral tetracyclines/macrolides

Tetracyclines are used extensively in the treatment of MGD and ocular and facial rosacea. Oral macrolides may be considered when tetracyclines are contraindicated, or in the event of unacceptable adverse reactions. More recently, a topical macrolide, azithromycin, has been developed.[122]

Tetracyclines (tetracycline, doxycycline and minocycline) have properties that are useful in

the management of DED. In addition to their antibacterial properties, these drugs also inhibit bacterial lipases, thereby reducing production of free-fatty acids in the lipid component of MG secretions and the tear film.[91] They also have anti-inflammatory properties, including inhibition of matrix metalloproteinases (MMP), phospholipase A2, and collagenase. The anti-inflammatory effects can also prevent the development of new blood vessel formation (corneal neovascularization) in rosacea.

The most commonly used tetracycline in eye care is doxycycline, which may be given at a dose of 40 or 50 mg once daily for MGD.

Patients with contraindications to tetracyclines, including children and pregnant or nursing women, may benefit from a course of an oral macrolide antibiotic, such as erythromycin or azithromycin, although the dosage and time course have not been well studied.[123, 124]

Lacrimal occlusion

Tear retention by lacrimal occlusion decreases symptoms, reduces corneal staining, prolongs TBUT, increases goblet cell density and decreases tear film osmolarity.[125, 126]

It is intuitive to consider lacrimal occlusion in patients with aqueous deficiency. Consider lacrimal occlusion for patients with <15 mm of wetting, and especially for patients with <10 mm wetting on the PRTT/CTT.

Control of inflammation is an important consideration. Impaired tear drainage may prolong the contact of pro-inflammatory mediators with the ocular surface. Conversely, tear film osmolarity may decrease and attenuate the inflammatory cascade. Normally, MGD and ocular surface inflammation should be controlled by a course of anti-inflammatory treatment before lacrimal occlusion is undertaken. However, this may be challenged in cases of severe aqueous deficiency (e.g. PRTT < 5 mm), when lacrimal occlusion is required to facilitate tear retention earlier in the course of treatment of a very dry eye.

Lacrimal occlusion is also indicated in CL intolerance, filamentary keratitis, neurotrophic corneae (with or without keratitis), cranial nerve VII (CN7) palsies and systemic diseases such as SS, Stevens-Johnson syndrome, graft versus host disease (GVHD), and others.

For patients with an occluded canaliculus, active canaliculitis, allergies to the materials, or frank punctal ectropion, lacrimal occlusion is contraindicated.

The most common complication is spontaneous extrusion of the plug(s) which necessitates replacement. Other complications include internal migration of punctal plugs, the inability to irrigate intracanalicular plugs, and pyogenic granuloma formation.[125, 126]

Meibomian gland expression

Although MG expression is a diagnostic procedure that reveals the quality and quantity of secretions (see previous section), it is also a therapeutic procedure that promotes normal gland function. Techniques include simple application of pressure to the lid[127] or placement of a metal object (e.g. Mastrota paddle) behind the lid to reduce pressure on the globe.

A novel thermal pulsation system for MG expression is available (LipiFlow®). The system heats the MG and expresses their secretions using a pulsatile inflatable cup. Symptoms and some objective signs (MG secretions, corneal staining and TBUT) improve with a single treatment and may be maintained for up to 9 to 12 months.[128] Further study is needed to determine the outcomes of single and repeated treatments.

Sleep masks and lid taping

Patients in whom lid closure is inadequate, especially during sleep, may benefit from lid taping, night-time masks or patches. Patients must be instructed on proper technique to protect the vulnerable ocular surface from trauma.

MANAGEMENT OF RECALCITRANT DISEASE

Ocular

Scleral contact lenses

Traditional contact lenses are generally avoided in patients with severe DED disease, except to act as bandage lenses for patients with a high degree of corneal staining.[129] However, scleral lenses, commonly used for treatment of an irregular cornea, may also be used for treatment of severe DED, including SS, neurotrophic keratitis and other surface disorders. A number of different lenses, including scleral lenses, have been used to treat patients with SS, irregular astigmatism, exposure keratitis, and other ocular surface conditions.[130, 131] All types of scleral lenses are designed to protect and heal the ocular surface, and to improve vision. They are suitable in addition to standard treatments.

Materials that allow high oxygen delivery and a limited amount of clearance under the lens are required in order to promote corneal and conjunctival metabolism, especially in the presence of altered endothelial cells. Patients with severe disease benefit from large diameter lenses (18-20 mm) while those with less severe disease may use mini-scleral lenses (14.5 to 16 mm), which are easier to fit and to handle.[132]

Topical medications, including anti-inflammatories, can be used concomitantly with scleral lenses. Scleral lenses are available in designs made for regular corneae as well and can be used to address episodic eye dryness related to contact lens wear. Well fitted scleral lenses may provide the same comfort as soft lenses, and provide the same quality of vision as gas permeable lenses, but offer the unique advantage of preserving hydration over time.[133, 134] By bathing the cornea on a constant basis, they can help to improve the patient's comfort and alleviate end-of-the day dryness.

Autologous serum eye drops

Autologous serum eye drops are made from the liquid component of the patient's own blood and contain a number of components found in natural tears that are involved in maintenance of the ocular surface, such as epidermal growth factor, transforming growth factor B, fibronectin, vitamin A and cytokines.[135]

Autologous serum eye drops are generally reserved for patients with severe disease whose treatment options have been exhausted. This is due, in part, to cost, but also to the lack of regulatory standards for serum preparation and storage, and to a paucity of data on which to standardize indications, to establish risks and contraindications, and to guide patient selection.[136] There are few centres that offer this therapy, and those that do are generally located in teaching hospitals. Autologous serum eye drops promote healing of the cornea with few adverse effects; however, the preparation, concentration (20%, 50%), and dosing frequency and duration are not standardized.

Amniotic membrane transplants

Sutureless amniotic membrane transplants (ProKera®, Biotissue) are an option for patients with severe recalcitrant DED and other ocular surface disorders. The device consists of a piece of amniotic tissue held in place by two clear, flexible rings. Healing of corneal lesions has been reported in 44 to 70% of patients depending on the indication.[137, 138] Some patients experience discomfort after placement of the device and recurrence of the primary pathological condition.

Tarsorrhaphy

Tarsorrhaphy may be a temporary or permanent procedure used to narrow the palpebral fissure in patients with non-healing ocular lesions associated with corneal exposure, severe dryness and loss of corneal sensitivity. Graves disease and CN7 palsies are examples of conditions that can cause extreme corneal exposure. Severe dryness may occur with or without systemic disease, but classic examples that may require surgical interventions include Stevens-Johnson syndrome, ocular cicatricial pemphigoid, and SS. Corneal hypoesthesia or anesthesia also puts the cornea at risk as does the inability to heal in conditions such as post-corneal surgery, radiation keratopathy and recurrent or recalcitrant neurotrophic ulcers.[139]

Systemic treatments

Secretagogues

The muscarinic agonist pilocarpine (Salagen®, 5mg) is indicated for the treatment of dry mouth in patients with SS. Use of this oral formulation is limited due to its adverse effect profile and its q.i.d. dosing. Many patients experience significant adverse effects such as excessive sweating (hyperhidrosis, in over 40% of patients), flushing, chills, nausea, and rhinitis especially at the maximum dose. For this reason it is advisable to start with one daily dose for one to two weeks, then increase to b.i.d. and so on, to allow the patient to become accustomed to the medication. Many patients are unable to reach the full dose, but may be helped by smaller amounts of the drug.

Immunosuppressants

Some immunosuppressive therapy improves symptoms in patients with SS; however, no agents are currently approved for use in this condition. Rituximab has shown some promise by improving salivary flow rate, symptoms, some ocular signs, as well as extraglandular manifestations and some laboratory parameters.[140]

CONCLUSIONS

By defining a more intuitive approach to clinical assessment (episodic, chronic, recalcitrant), the authors hope to help practitioners in the effective assessment and management of the many patients who present to clinical practice with varying levels of symptoms and signs of DED. Beginning with a screening process that involves a series of key questions and an understanding of the predisposing factors that contribute to DED, doctors can more readily differentiate DED from the many conditions that mimic the symptoms. A full DED workup is recommended after screening to confirm the diagnosis, as well as to identify any co-morbidities. Armed with this information, the clinician can readily develop a treatment plan tailored to each patient's condition.

A great deal has been learned about the complexity of DED in the last two decades. The awareness of the inflammatory model of DED is growing, as is the understanding of the long-term management of this spectrum of conditions. Contemporary use of anti-inflammatory treatments has dramatically improved our ability to positively affect patient experience of this chronic disease. Current investigations focusing on the inflammatory model will lead us to future treatment options, and the ability to further improve the quality of life of patients with DED.

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SUPPLEMENTARY APPENDIX

ADJUNCT TESTING AND EMERGING TECHNOLOGIES

The tests described in this section represent emerging technologies that the practitioner may find useful for performing certain assessments in select patients. The Supplementary Table summarizes the equipment that is useful in a dry eye disease (DED) clinic, and includes the time required to administer the test and, where available, the sensitivity and specificity of each test.

NASOLACRIMAL ROUTE PATENCY

The Jones test involves the assessment of the patency of the nasolacrimal duct.[141] Briefly, 2-3 fluorescein strips are placed in the eye and the patient is asked to blink several times to allow the fluorescein to enter the nasolacrimal passageway via the punctum. The presence of fluorescein in the ipsilateral nostril indicates that the passageway is functional. This is a good additional test in patients that complain of epiphora (excessive tearing) to rule out if the nasolacrimal route is blocked.

EVALUATION OF TEAR OSMOLARITY

Osmolarity measures the concentration of ions or particles in fluids such as tears.[8, 142, 143] Osmolarity testing should be performed prior to any other test that requires tear and/or lid manipulation, so as not to potentially affect the results of subsequent tests.

All fluids in the body, including tears, have electrical conductivity properties, depending on the ionic content of the tissue. Any change in the concentration or composition of ions, such as in DED, will affect conductivity. The TearLab Osmometer[144] measures tear film osmolarity using electrical impedance in a 50 nL sample obtained from the lower tear meniscus.

The osmolarity value indicates the severity of DED. A value of more than 308 mOsm/L is indicative of DED and asymmetry between the two eyes is expected, especially with increasing severity.[144-146] Measurements less than 308 mOsmol/L indicate no DED.

The unit has two handles, one for each eye. The individually-packaged disposable tips are inserted onto the handle, after which there is a 2-minute time window to take the measurement. The tip is lowered gently onto the lower temporal tear meniscus and the appearance of an indicator light and an auditory prompt indicates that the required amount of tears (50 nL) has been collected. The handle is then docked onto the base and a reading of the osmolarity is given within a few seconds.

The instrument is user friendly with a quick learning curve (2-3 patients). It is advised to leave the instrument on during the week, as older units take 20-25 minutes to initialize. The newer models only require 5 minutes. Calibration of the unit is recommended every time you open a new box of tips (42 tips/box).

Supplementary Figure 1. *TearLab osmometer.*

Supplementary Figure 2. *TearLab osmometer handle and tear sampling from lower temporal tear meniscus.*

LIPID LAYER ASSESSMENT

Specialized instruments are available to view the lipid layer of the tear film specifically, which is becoming increasingly important as evaporative DED becomes a more prominent concern. The Tearscope (Keeler) uses Ganzfeld-type illumination to view the lipid layer while at the slit lamp and provides a subjective assessment of the thickness of the lipids.[147-149] This instrument is no longer commercially available. The LipiView/LipiFlow® system[56] uses interferometry to view the thickness and quantity of the lipid layer. A lipid layer thickness profile is calculated, which provides an indication of the potential for evaporative DED. The instrument comprises two components, LipiView and LipiFlow®, the latter of which is a therapeutic component (see section on treatment).

The lipid layer creates an interference pattern on the ocular surface that can be used to estimate its thickness. The LipiView system uses interferometry to assess the thickness profile of the lipid layer which can be used diagnostically, and to monitor treatment or post-surgical outcomes.

INFLAMMATORY BIOMARKERS

MMP-9 is a non-specific marker of inflammation that is typically found in very low concentrations on the ocular surface in normal individuals and in higher levels in patients with inflammation, such as DED.[150, 151] InflammaDry® measures MMP-9 levels on the ocular surface within 10 minutes of tear collection.[152] An MMP-9 level >40 ng/mL is highly correlated with moderate to severe DED.

MEIBOMIAN GLAND ASSESSMENT

Supplementary Figure 3. *InflammaDry® used to collect tears from the lower conjunctiva for analysis of MMP-9 biomarker.*

The Keratograph (Oculus®) is one of the latest emerging technologies for the assessment of the cornea and tear film. The instrument includes a corneal topographer, an infrared light MG evaluator (Meibo-Scan), and tools for measuring tear meniscus height (TMH), non-invasive TBUT assessment, bulbar conjunctival redness and tear film dynamics.[50] The Meibo-Scan allows the practitioner to assess the linearity and regularity of the MG in both lids. Information regarding how bent or curved the MG are may point towards early signs of MG problems.[153-156]

Supplementary Figure 4. *Keratograph 5M (Oculus).*

Supplementary Table. *Summary of equipment.*

Test	Manufacturer	Time to administer	Sensitivity	Specificity
OSDI	Allergan	< 1 min	80%	79%
McMonnies	N/A	< 1 min	98%	97%
DEQ-5	Indiana University	< 1min	90% (if score >6)	81% (if score >6)
TearLab Osmometer	TearLab	<2 min		
Schirmer	Several available	5 min	85%	83%
CTT/PRTT (ZoneQuik)	Menicon	15 sec	86%	83%
Mastrota Paddle	Ocusoft	<1 min	N/A	N/A
MG Evaluator	Tearscience	<1 min	N/A	N/A
Ophthalmic dyes	Several available	<2 min	N/A	N/A
Yellow Barrier filter	Most GP CL labs	<1 min	N/A	N/A
InflammaDry	Labtician	10 min	85%	94%
Keratograph	Oculus	5-10 min depending on test performed	N/A	N/A
LipiView System	Tearscience	LipiView: <5 min	N/A	N/A