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Diagnosis and management of dry eye

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ABSTRACT

Dry eye is one of the most important causes of ocular discomfort and fluctuating vision. Eye care practitioners may face challenges in accurately diagnosing and appropriately managing dry eye because the signs and symptoms are similar to other conditions. This review article discusses different techniques for diagnosing dry eye and contemporary approaches to its management.

INTRODUCTION

The International Dry Eye Workshop (DEWS) has defined dry eye 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[1]. "The two main classifications of dry eyes are increased evaporative loss and aqueous deficient dry eyes. Increased evaporative tear loss is associated with eyelid disorders and meibomian gland dysfunction (MGD), as well as exposure, contact-lens wear, and environmental situations[1]. Aqueous deficient dry eye comprises a range of disorders and is subdivided into groups, with and without lid margin disease, as well as tear distribution abnormalities[1]. It is estimated that dry eye prevalence ranges from 5% to more than 35%, and often coexists with other diseases such as Sjögren's syndrome (a chronic systemic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs) and keratitis sicca[2].
Other aetiologies of dry eye include drugs such as anticholinergics, antihistamines and birth control pills. The most common clinical presentation of dry eye includes irritation, dryness, burning, itching, tearing, and crusting[3]. Dry eye problems also pose a challenge to successful wearing of contact lens wear and it is important to identify and treat dry eye problems prior to fitting contact lenses. Mild or moderate cases of tear deficiency often can be managed with tear supplementation or by tear conservation. More severe cases of tear deficiency such as in rosacea and MGD may complicate contact lens wear[4].

Dry eye is often misdiagnosed and overlooked because its clinical presentation is not specific to dry eye only, and some patients with ocular allergy, blepharitis, and irritative nonallergic conjunctivitis may also complain of similar signs and symptoms. In addition, there is usually a lack of concordance between bothersome ocular symptoms and clinical findings of dry eye on examination[3]. Therefore, a detailed patient history to characterise symptoms and to identify aetiological causes, and a comprehensive ocular evaluation of the periocular skin and lids, ocular and tear film, should be conducted. All reasonable clinical evaluations should be explored when examining a patient suspected of having a dry eye, particularly those wearing contact lenses. Although the severity of symptoms vary from one patient to another and may not correspond to the level of ocular surface damage with dry eye, it is still important to gauge the intensity and effect of a patient's symptoms. The case history should include questions to elicit functional or quality-of-life consequences of dry eye, as well as description specific symptoms in certain environments[4]. Factors associated with dry eye such as dermatologic diseases, environmental and occupational factors, medication or supplements, ophthalmic and systemic diseases should be identified[4]. This information will guide the clinician to provide an appropriate therapeutic and management for the dry eye patient. The quality of life of patients with dry eye can be affected by severe discomfort caused by dryness and burning sensation, vision fatigue and even reading difficulties in some cases. Two validated questionnaires, the Ocular Surface Index (OSDI) and the Standard Patient Evaluation of Eye Dryness (SPEED) have been developed to assess dry eye disease symptoms and the OSDI specifically explores different aspects of the disease on vision-related activities. It is therefore suggested that eye care providers download these questionnaires and administer them on their patients to explore the impact of dry eye disease.

These documents can be downloaded from the following web sites: http://dryeyezone.com/encyclopedia/documents/OSD.pdf http://korbassociates.com/assets/SPEED_Questionnaire.pdf.

Tear film composition

The preocular tear film (POTF) is composed of three layers; namely the lipid, aqueous, and mucus layers[5]. The outermost lipid (oily) layer is produced by the meibomian glands (which are embedded in the tarsal plates) and the Zeiss and Moll glands of the eyelid margins[5]. The main function of the oily layer is to stabilize and retard the evaporation of the bulky aqueous layer, and to contain the aqueous phase of the POTF by reducing surface tension[6]. Diseases such as blepharitis alter the high molecular weight and low polarity properties of the POTF, leading to ocular surface disorders and symptoms of dry eye[6].
In addition, patients with MGD may have reduced or altered meibomian secretions, resulting in lipid layer abnormalities[6]. The aqueous layer makes up about 90 percent of the POTF and is mainly produced by the accessory exocrine lacrimal glands of Krause and Wolfring[7]. A reduction in aqueous production as seen in Sjögren's syndrome, keratitis sicca, increasing age and hormone replacement therapy will result in symptoms of aqueous deficient dry eye such as foreign-body sensation and lacrimation/tearing[4]. The clinical presentation of aqueous deficient dry eye includes reduced tear meniscus, reduced tear breakup time, decreased wetting on Schirmer testing, ocular surface staining, as well as debris and strands of mucous in the tear film (which can lead to the formation of filamentary keratitis in advanced cases)[4]. Dacryoadenitis, facial nerve paralysis, chemical burns, congenital alacrima, gamma radiation, antihypertensives (diuretics, adrenergic antagonists, and beta-blockers); antihistamines (especially first-generation H-1 inhibitors); medications that have anticholinergic effects (tricyclic antidepressants, phenothiazines, etc.); can also adversely affect tear production[8]. The innermost layer of the POTF is the mucus layer and the major contribution of this layer comes from the goblet cells of the conjunctiva[5]. The mucus layer is primarily responsible for lubricating the lids and serves as an adsorbing interface between the aqueous layer and the hydrophobic corneal epithelium[5]. Reduction in the number of conjunctival goblet cells, resulting in a decrease in mucin production, can be caused by conditions that damage the conjunctiva. Allergic conjunctivitis, ocular cicatricial pemphigoid, Stevens-Johnson syndrome, severe trachoma, or chemical (especially alkali) burns and vitamin A deficiency (seen mostly in developing countries) can result in impaired goblet cell function causing mucin deficient dry eye[8]. Although neural receptors mechanisms may be involved, tear film break up is based partially on thinning of the aqueous layer and subsequent contact between the lipid and mucin layers[4].

Clinical ocular examination

The clinical examination should start with an external ocular evaluation with and without the slit-lamp biomicroscope, and include, but not limited to, the following[4]:

1. External view of the eye, noting lid structure, position (lagophthalmos), symmetry, and blink rate and dynamics.
2. Biomicroscopic examination of the lid margins (checking for redness, telangiectasia, thickening, debris or collarettes, mites) and eyelashes (checking for missing eyelashes, blepharitis), meibomian gland orifices (checking for obstructions), and their contents (is it clear normal oily liquid or is it opaque and thick).
3. Biomicroscopic examination of the tear film to identify mucus, debris, interference patterns in the lipid layer, and tear film meniscus height.
4. Biomicroscopic examination of the cornea and conjunctiva, both with and without sodium fluorescein and lissamine green staining. The ocular surface staining patterns provide useful diagnostic clues. For example, changes in tear film stability may manifest as reduced and inconsistent breakup time while in more severe cases, tear film debris may be accompanied by corneal mucus strands, filaments, furrows, dellen, staining, or erosion. The conjunctiva may be red and have folds particularly in the lower temporal area, where the eyelid meets the globe.

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Dry eye tests

An important aspect of the examination is assessment of the integrity of the lacrimal system. There are several available technologies that allow for the assessment of tear osmolarity, thickness of the tear film lipid layer, and an inflammatory marker of dry eye[4]. However, no single tear quantity or tear quality test is capable of assessing the integrity of the tear film or ocular surface[4]. Invasive techniques usually do not provide realistic measures because of the 'stimulation' involved. For example, fluorescein instillation may cause reflex tearing. Any measurements made in such circumstances must be treated with suspicion and should not be regarded as being representative of 'normal'. Non-invasive techniques may still involve instillation of stains (dyes) but they either do not stimulate reflex tearing or their effects can be accounted for in the final assessment. A variety of invasive and non-invasive techniques used to measure the tear characteristics will be discussed below. Tear quantity tests are useful in confirming the diagnosis of aqueous-deficient dry eyes and the most frequently utilised procedures are: Schirmer's tear test, phenol red thread test, fluorescein-enhanced assessment, evaluation of the tear prism height, tear film debris, rose bengal/ lissamine green staining.

1. Schirmer's tear test: assesses aqueous secretion using special-purpose sterile filter strips. The strips are bent at the notch and placed in each cul-de-sac (of the lower lid margin) without anesthetic (Schirmer I) to evaluate the quantity of the aqueous tear layer produced during a fixed time period[5]. The patient is instructed to look up both before insertion of the filter strip and during the 5 minute test. Blinking is permitted during the test. After waiting for 5 minutes, a measurement of the amount of wetting is done. Adequate aqueous secretion is indicated when more than 15 mm of the strip is wet in 5 minutes[4, 5]. Schirmer II (with topical anesthetic) or basic secretion test is a modification of Schirmer I test because a topical anesthetic is applied in this test. The procedure is similar to Schirmer I test and the normal reading is > 5 mm of wet strip in 5 minutes[4, 5].

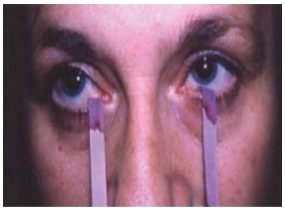

Figure 1: Schirmer's test, showing strips placed in the lower eyelid pouch

2. Phenol red thread: This is a rapid basal tear volume assessment test that is less irritating to the eye and requires no anesthetic. By incorporating the pH-sensitive phenol red (phenolsulphophthalein) in the thread, the pH of tears can be determined as the same time[5]. A 70 mm length red-impregnated special 2-ply cotton thread is inserted into the lower cul-de-sac for 15 seconds and the eyes are closed immediately after insertion[4]. The wet length is measured and the colour change noted. An average wet length of 16.7 mm was found for a large population (3780 eyes) of 'normals' in 15 seconds and wet length of less than 6 mm are suggestive of dry eye[5]. The colour changes from yellow to bright orange due to the alkaline nature of tears[5].

3. Fluorescein-enhanced assessment: This test involves instillation of fluorescein to the ocular surface, and observing the rate of dilution of the aqueous component of the POTF, using the cobalt-filtered illumination of the slit-lamp biomicroscope[5]. The cobalt-filtered illumination also allows for the observation of subclinical disruption of the ocular surface[5].

4. Evaluation of the tear prism height: This is a simple and quick test that assesses the tear meniscus height with a biomicroscopic examination both with and without instilling fluorescein dye[9]. A tear meniscus height greater than 0.2 mm is considered normal and a height of < 0.1 mm is associated with dry eye[9].

5. Tear-film debris: Excessive particulate matter in the tear film, visible by biomicroscopic examination, may indicate inadequate flushing action due to reduced tear flow[4].

6. Rose bengal/lissamine green: This stains devitalised and dehydrated tissues of the conjunctiva and cornea, associated with insufficient tear flow, as reddish purple areas[10]. Observation is done through the white light of the slit-lamp biomicroscope. A scoring system for rose bengal staining assigns values of 0 to 3 for each of the lateral and medial corneal and conjunctival regions of the exposed intrapalpebral ocular surface. A value of 0 indicates absence of staining and maximum score of 9 indicates severe rose bengal staining[4, 10]. Lissamine green stain works on the same principle as rose bengal but it is less irritating to the patient and is therefore preferable. A negative corneal staining pattern with a vague mosaic pattern is diagnostic of anterior basement membrane dystrophy, which can lead clinicians to make an erroneous diagnosis of dry eye[10].

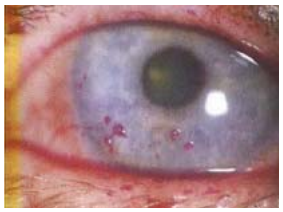

Figure 2: Rose bengal stain stains areas of devitalised tissue (seen as a purple colour)

7. Lacrimal equilibration test (LAT): This test assesses the function of the lacrimal system. It works on the principle of "stressing" the lacrimal system due to instillation of celluvisc thereby increasing tear volume and viscosity. Celluvisc is instilled into the eye and the time taken by the patient to be able to read their threshold visual acuity is noted[5]. Asymptomatic patients are able to read their threshold visual acuity in less than 5 minutes and those with dysfunction lacrimal system take longer than 5 minutes[5]. Other tests that may be used to evaluate tear quantity are fluorophotometry and temporary punctal occlusion. Several procedures are commonly used clinically to evaluate tear film stability, with break up time and tear thinning time being the most popular.

1. Tear film break up time (TBUT): tests aqueous volume and the integrity of the mucin layer[11]. TBUT is the time taken (in seconds) for the first break in the tear film ('dry spot') to appear following a complete blink[11]. It is performed by instilling fluorescein into the eye and the patient is instructed to blink fully and then stop blinking. At this point, the timing commences. The whole of the exposed tear film is observed and the time at which the first break appears is noted. Tear film breaks appear as dark spots or streaks indicating a disruption of the whole tear film[11]. The normal time required for the tear film to break up following a blink is approximately 15-20 seconds and average readings range from 10-40 seconds. TBUT values of less than 10 seconds are suggestive of an abnormal tear film. Recommendation for successful contact lens wear is a TBUT of greater than 10 seconds[11]. Noninvasive TBUT (NIBUT) is performed without the addition of fluorescein to the tear film. White light of the slit-lamp or a Tearscope™ can be used to observe the tear film. Clinical experience suggests the light source of the slit-lamp generates heat, causing evaporation of the tear film which may affect NIBUT while the Tearscope™ uses cold light source which allows for a truer estimation of the NIBUT.

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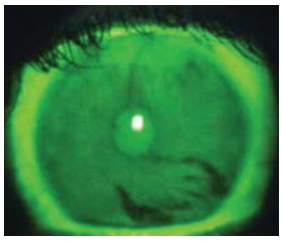

Figure 3: Dry spots (tear film break film) are indicated by the dark areas in the lower right corner

2. Tear-thinning time (TTT) is a non-invasive test that uses a keratometer to view the mire image. While a blink is held, the keratometer's mire images are observed and the time of the first disturbance or distortion of the mire images is noted[12]. Any disturbance of the mire image is attributed to alterations of the tear film[12]. Normal values for TTT have been reported to be 18.5 ± 6 seconds. Other tests that may be used to evaluate the quality of the POTF are: impression cytology, conjunctival scraping and biopsy and ELISA tear protein profile.

Table 1 summarises the common tests performed to assess for dry eye disease and also lists the normal values that have been established for selected tests.

Test	Invasive (I) or Non-Invasive (NI)	Significance	Equipment to test /assess	Normal values
Schirmer I (without anaesthesia)	I	No diagnostic value	Schirmer strips	>15 mm in 5 minutes
Schirmer II basic secretion test (with anaesthesia)	I	Aqueous deficiency when reduced (accessory lacrimal gland dysfunction)	Anesthetic, Schirmer strips	>5 mm in 5 minutes
Phenol red thread test	I	Tear volume	Phenol red thread	>16.7 mm in 15 seconds
Tear meniscus height	I or NI	Aqueous quantity	Biomicroscope	Range: 0.1 - 0.6 mm
Tear film osmolality	I	Lacrimal gland function	Osmometer	<312 mOsms /L; ≤316 mOsms/L[b]
Lactoferrin	I	Lacrimal gland function	Laboratory analysis	1.42 mg/mL (<1.00 mg/mL is abnormal)
Rose bengal/lissamine green	I	Non-mucus-coated	Dye, Biomicroscope	0 = No staining visible 9 = Severe staining
Fluorescein	I	Microepithelial defects/mucus deficiency	Biomicroscope	No staining visible
Interference fringe pattern	NI	Lipid layer integrity	Biomicroscope	Uniform biomicroscopic appearance
Meibomian gland expression	NI	Meibomian gland function	Biomicroscope	Clear
TBUT	I	Tests integrity of the Tear film stability/mucus deficiency	Biomicroscope, fluorescein	>10 seconds
NTBUT	NI	Microepithelial defects /aqueous adequacy	Biomicroscope/ Tearscope™	40 seconds
TTT	NI	Tear stability	Keratometer	18.5 ± 6 seconds
Jones I	I	Lacrimal drainage system	Fluorescein	Dye appearance
Jones II	I	Lacrimal drainage system	Fluorescein, Biomicroscope	Dye appearance
Lacrimal equilibration time	I	Lacrimal drainage system	Celluvisc/Teargel	Reach threshold visual acuity within 5 minutes

TABLE 1: Tear function tests and normal values[4]

Treatment and management of dry eye

The primary goal of treatment is to offer comfort and relieve symptoms, heal ocular surface and prevent complications such as ulcers, thinning, scarring, and neovascularization.

Tear supplementation

Tear supplementation may suffice to relieve symptoms of dry eye. Frequent administration (6-10 times daily) with ocular lubricant drops is effective for mild to moderate cases of dry eye[13]. Ocular lubricant gels have an increased contact time and add viscosity and volume. Ocular lubricant ointments are composed of petrolatum, lanolin and/or mineral oil, and are usually used at bedtime because of blurred vision following instillation. Extended wear bandage soft contact lenses can be used. If the dry eye is due to blepharitis or MGD, lid hygiene is necessary. Lid hygiene can be performed with a commercially available lid scrub formulation or by using dilute baby shampoo (1:10 in water) applied with a facial cloth[4]. Thermal pulsation therapy, golf club spud, intra-ductal probing relieves meibomian gland obstruction[14].

Tear conservation

Tear evaporation can be reduced by using ointment, environmental control measures, goggles, moisture chambers, humidifiers and tarsorrhappy. Puntal occlusion with temporary or permanent plugs blocks the drainage channel of tears[15]. Temporary collagen implants are used first to test efficiency and therefore symptoms and course need to be re-assessed. Temporary occlusion can be achieved by using two categories of plugs; collagen rods and extended dissolvable/synthetic plugs. Collagen rods are 0.2-0.6 mm in diameter and dissolve in 4-7 days[16]. Temporary synthetic plugs dissolve in approximately 2-6 months and are used for post-surgical dry eye[16]. Permanent occlusion is achieved by using silicone, smart, and form fit plugs as well as surgery/cautery. Silicone based plugs include Herrick/intracanalicular (0.3-0.7 mm) and Freeman (0.3-1.0 mm) plugs. It is important to note that intracanalicular plugs can be removed by irrigation and Freeman plugs can be removed by using forceps. Adverse reactions of silicone plugs include extrusion, epiphora, subconjunctival haemorrhage, pyogenic granuloma, infection and dacryocystitis[16]. Other permanent plugs include smart and form fit plugs. Smart plugs are rigid at room temperature and becomes a soft and flexible elastic gel at or above 37 degrees celsius[4].

The form fit plugs expands into a soft, pliable, gelatinous material when it comes into contact with tears[4]. Once inserted into the punctum, it then hydrates over 10 minutes and increases in size until it fills the vertical canaliculi. It is removable by irrigation[4].

Tear stimulation

Oral pilocarpine HCL (Salagen) is a parasympathomimetic with muscuranic secretagogue effect, which improves lacrimation[4].

A 5mg oral dosage of pilocarpine taken four times a day is used in Sjogren syndrome and radiation induced xerostoma[4]. Possible side effects include sweating, nausea and flush.

Diagnosis and management of dry eye

Anti-inflammatory drugs

The mainstay drugs for dry eye treatment include anti-inflammatory drugs such as steroids and cyclosporin. Corticosteroids provide an effective anti-inflammatory treatment for dry eye[17]. Steroids are associated with the development of serious ocular adverse effects such as cataract formation and intraocular pressure (IOP) elevation and these limits their long-term use.
Cyclosporin 0.05% ophthalmic emulsion (Restasis) is an immunomodulator and exerts its anti-inflammatory effects by preventing T cells from releasing cytokines[18]. It improves tear volume production and is indicated for the treatment of dry eye secondary to inflammation associated with keratitis sicca, Sjögren's syndrome, rheumatoid arthritis and lupus[18]. Cyclosporin is lipophilic and the hydrophilic corneal stroma creates a penetration barrier into the eye, thereby limiting intraocular adverse effects[18]. It produces significant improvement after 6 month of use. It is however, ineffective if there is diffuse loss of goblet cells such as in ocular pemphigoid, Steven Johnson syndrome and chemical burns[18]. Cyclosporin is contraindicated in ocular infection. Reported side effects include ocular itching, mild ocular hyperaemia, epiphora, eye pain, foreign body sensation, itching and blur[18].

Antibiotics

Anterior blepharitis usually is the direct result of disruption or infection of the lipid-producing glands that open to the lid margin. Erythromycin, bacitracin, polymyxin B-bacitracin, gentamicin, and tobramycin are all effective antibiotics for treatment of staphylococcal blepharitis[4]. Tetracyclines and doxycycline are also effective for treating patients with MGD.
Neither tetracycline nor its derivatives should be given to children under the age of 8 years or to pregnant or nursing women.

Nutritional supplements

Omega 3 and flax seed oil reduces T lymphocyte proliferation while omega 6 can produce anti-inflammatory and pro-inflammatory products[19].

Mucolytic agents

Mucolytic agents softens mucous and have intracellular effect on goblet cells. A mucolytic agent such as N-acetylcysteine disrupts formation of filaments and may increase TBUT by altering lipid secretions[20].

Hormones

There is negative correlation between testosterone and tear production, and a positive correlation between oestrogen and tear production in premenopausal individuals[21]. In menopausal individuals, a positive correlation exists between testosterone and tears production, and a negative correlation exists between oestrogens and tears production[21]. At any age, there is a negative correlation between prolactin and tear production[21]. Treatment options used in dry eye, their effects, examples and adverse effects are summarised in Table 2.

Surgical

When medical treatment remains ineffective and ocular symptoms deteriorates, surgical procedures such as laser puntoplasty and dacryocystorhinostomy should be considered. Laser puntoplasty is a form of permanent punctal occlusion using a heat-generating laser to create scar tissue.
Dacryocystorhinostomy involves a direct drainage from the lacrimal sac to nasal passage.

CONCLUSION

Dry eye is a serious condition as it impacts negatively on the quality of life of the sufferer by producing severe symptoms and complications. The history, symptomatology and examination are important to enable an accurate diagnosis of dry eye and to establish its underlying causes. The most common presenting signs and symptoms of dry eye are irritation, dryness, burning, itching, and tearing, with treatment being tailored to address the severity of the signs and symptoms. Primary treatment algorithm include measures to supplement and conserve tears. Pharmacological agents such as steroids, cyclosporines, antibiotics are usually effective for dry eyes associated with inflammation. Surgical intervention is usually reserved for severe cases that are non-responsive to other therapies. Knowledge of techniques for diagnosing dry eye, treatment, and proper patient education, is important for the clinician to optimise patient care and outcomes for the long-term comfort of these patients.

Class	Effect	Examples	Adverse effect
Tear supplementation	Symptomatic relief	Cellufresh, Celluvisc, Teargel® (Restan)	Sensitivity to preservatives
Tear conservation	Symptomatic relief	Moisture chamber goggles, Puntal plugs	Epiphora, scarring, decreased lacrimal function (Puntal occlusion)
Tear stimulation	Tear production	Pilocarpine	Sweating, nausea, flush
Corticosteroids	Reduces inflammation	Fluorometholone, Dexamethasone, Prednisolone, Loteprednol etabonate	Increases in IOP, cataracts formation, delayed wound healing, and increased susceptibility to infection
Cyclosporine	Modulates inflammation, increases tear production	Cyclosporine 0.05%	Stinging and burning upon instillation
Antibiotics	Anti-infective	Bacitracin, Azithromycin, Tetracycline, Doxycycline	Gastrointestinal effects (Tetracycline & Doxycycline), Photosensitivity, Pseudotumor cerebri (Doxycycline)
Nutritional	Reduces inflammation	Omega 3 and 6 fatty acids	Gastrointestinal effects
Mucolytic	Increase TBUT	N-Acetylcysteine	Nausea and vomiting
Hormone replacement	Increase tear production	Testosterone, Oestrogen	Sleep apnea, acne flares

TABLE 2: Treatment of dry eye diseases[4, 13-21]

For a complete list of the references; please contact Shannon: 0832601036