

Dry Eye and Clinical Disease of Tear Film, Diagnosis and Management

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Abstract

Dry eye disease (DED) is a clinically significant multifactorial disorder of the ocular surface and tear film as it results in ocular discomfort and visual impairment and predisposes the cornea to infections. It is important for the quality of life and tends to be a chronic disease. It is also common, as the prevalence is estimated between 5 % to 30 % and this increases with age. Therefore, it is recognised as a growing public health problem that requires correct diagnosis and appropriate treatment. There are two main categories of DED: the deficiency of tear production (hyposecretive), which includes Sjögren syndrome, idiopathic or secondary to connective tissue diseases (e.g. rheumatoid arthritis), and non-Sjögren syndrome (e.g. age-related); and the tear evaporation category, where tears evaporate from the ocular surface too rapidly due to intrinsic causes (e.g. meibomian gland disease or eyelid aperture disorders) or extrinsic causes (e.g. vitamin A deficiency, contact lenses wear, ocular allergies). Management of the disease aims to enhance the corneal healing and reduce patient's discomfort. This is based on improving the balance of tear production and evaporation by increasing the tear film volume (lubrication drops) and improving quality of tear film (ex omega-3 supplements, lid hygiene, tetracyclines), reducing the tear film evaporation (paraffin ointments, therapeutic contact lenses), reducing tear's drainage (punctal plugs, cautery) and finally by settling down the ocular surface inflammation (steroids, cyclosporine, autologous serum), as appropriate. In this article we will review the clinical presentation, differential diagnosis and treatment options for DED.

Keywords

Dry eye disease, tear film, Sjögren, ocular inflammation.

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There is now an increased recognition by clinicians that dry eye disease (DED) is a common disorder characterised by dryness and damage of the ocular surface. It affects quality of life, including aspects of physical, social and psychological functioning, because it induces ocular discomfort, burning sensation, light sensitivity, visual disturbances or even corneal erosions and infections. DED is also known as keratoconjunctivitis sicca, dry eye syndrome and dysfunctional tear syndrome.

DED prevalence has been reported to range from 5 % to 30 %, this being a likely result from differing study populations and DED definitions. In a large population study, Moss et al. reported the prevalence of dry eye to be 14.4 % in 3,722 subjects aged 48 to 91 years and noted that the prevalence of the condition doubled after the age of 59. As a consequence, DED prevalence is expected to increase in ageing populations, which will eventually make this health problem more prominent.¹⁻⁴

In order to address the problem, the International Dry Eye Workshop (DEWS) defines 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.³⁻⁵

Indeed, DEWS has recognised dry eye as a disturbance of the lacrimal functional unit, an integrated system comprising the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands) and lids, and the sensory and motor nerves that innervate them.^{3,4} Dysfunction of any component of the lacrimal functional unit may lead to ocular surface disease, related to inflammation and increased tear film osmolarity.

This multifactorial aetiopathogenesis explains why the clinical diagnosis of dry eye remains a challenge, not only due to the wide spectrum of alterations of the ocular surface with different aetiology and pathophysiology,⁵ but also due to the lack of well standardised diagnostic tests,⁶ and the fact that corneal surface is sensitive to external stimuli and, while the most diagnostic tests are overly invasive, the non-invasive tests are still considered expensive for everyday practice. Therefore, a holistic approach and a careful examination of tear film, cornea, eyelids, anatomically and functionally, as well as a thorough clinical history is needed to diagnose DED.^{3,5-8}

Early diagnosis of DED and identification of the underlying cause is essential not only for the management of the ocular surface disease, but also for the diagnosis and management of the systematic disease,

Table 1: Categories of Dry Eye Disease

Deficient Aqueous Production (Hyposecretive)
Sjögren Syndrome Dry Eye
Primary
Secondary
Non-Sjögren Syndrome Dry Eye
Lacrimal gland deficiency
Lacrimal gland duct obstruction
Reflex hyposecretion
Systemic drugs
Evaporative
Intrinsic Causes
Meibomian gland dysfunction
Disorders of lid aperture
Low blink rate
Drug related
Extrinsic Causes
Vitamin A deficiency
Topical drugs and preservatives
Contact lens wear
Ocular surface disease (e.g. allergy)

which might be occult, and may serve as a common link between ophthalmologists and physicians.^{9,10}

Causes – Differential Diagnosis

Multiple causes can produce either inadequate tear production or abnormal tear film constitution, resulting in excessively fast evaporation or premature destruction of the tear film.¹¹

To classify and categorise DED, DEWS developed a three-part classification, based on aetiology, mechanisms and disease stage, and further distinguished two main categories of dry eye states by cause: aqueous deficiency and the evaporation^{1,2} (see *Table 1*).

In both categories, tear film hyperosmolarity and subsequent ocular surface inflammation are thought to lead to the variety of symptoms and signs associated with dry eye, with a common mechanism. The increased osmolality of the tear film stimulates the expression of interleukin-1 β (IL-1 β), tumour-necrosis factor- α (TNF- α) and matrix metalloproteinase 9 (MMP-9), as already shown in *in vivo* animal models. These cytokines enhance mitogen-activated protein kinase (MAPK) cascades and subsequently stimulate the production of inflammatory cytokines and MMPs, resulting in DED.^{3,9} Excessive tear evaporation and reduced lacrimal tear secretion results in a vicious cycle of corneal inflammation and ocular dryness, as the aqueous tear pool is reduced.

Any form of lacrimal gland dysfunction or destruction may cause the cycle of reduced tear production, inadequate tear pool, hyperosmolarity of the tear film and inflammation of the ocular surface. The deficiency of aqueous tear production is further subclassified into Sjögren and non-Sjögren syndrome.^{3,11–15}

In Sjögren syndrome, the tear hyposecretion is secondary to an autoimmune infiltration and destruction of the lacrimal gland. This autoimmune exocrinopathy is considered as primary or idiopathic, or secondary – when a systemic connective tissue disease (CTD) is present, e.g. rheumatoid arthritis (most commonly), systemic lupus erythematosus, scleroderma, primary biliary cirrhosis, polymyositis,

dermatomyositis, Hashimoto thyroiditis, interstitial nephritis, Wegener granulomatosis and polyarteritis nodosa.^{16,17}

In non-Sjögren syndrome, the deficiency in the tear production is not related to a CTD. The primary type is typically connected to the age-related dry eye, or more rarely to congenital disease e.g. Riley-Day syndrome and familial dysautonomia.

The secondary type is related to lacrimal gland deficiency due to infiltration of the gland in sarcoidosis, lymphoma, amyloidosis, haemochromatosis, HIV, graft versus host disease, systemic vitamin A deficiency and lacrimal gland denervation.

Lacrimal gland obstructive disease is caused by trachoma, ocular pemphigoid, erythema multiforme and Stevens Johnson syndrome, ocular burns and post-radiation fibrosis.

Contact lens wearers, people with thyroid disease and people with diabetic neuropathy may suffer from corneal hypoesthesia, impaired sensory drive and subsequently decrease in the reflex tear production. This reflex sensory aqueous deficiency is additive to any structural and functional alterations that might coexist in the lacrimal gland.^{9,14,15,18–20}

Evaporative loss, which causes an unstable tear film and signs and symptoms of DED, without dysfunction of the lacrimal gland tear production, is more commonly related to meibomian gland dysfunction (MGD) or posterior blepharitis. Meibomian glands produce the lipid (outer) layer of the tear film, which protects the tear pool from evaporation. Thus, the dysfunction of meibomian glands causes evaporation of tear film.^{3,11} A significant clinical finding in this common condition is the normal or excessive positive Schirmer I test (more than 15 mm) with low tear break-up time (TBUT) measurement (less than 10 seconds) and a normal tear meniscus with only a small amount of debris, while in Sjögren syndrome aqueous deficiency, the main clinical measurement is the excessive decreased Schirmer test of usually less than 5 mm.^{21,22} In order to establish the diagnosis it is always important to correlate the tear film measurements with clinical signs, e.g. Rose Bengal/Lissamine green stains Marx's line (the mucocutaneous junction of the lid margin) in most eyes with MGD. Thyroid disease, when involving proptosis or lid retraction, and other ocular conditions with increased intra-palpebral aperture such as floppy eyelid syndrome and lagophthalmos, could also lead to evaporation loss.

Extrinsic causes of evaporative loss are the chronic use of contact lenses, allergic ocular surface disease, topical medications such as beta blockers, miotic agents and preservatives (e.g. benzalkonium chloride), which could decrease the goblet cell density and cause instability of the tear film layer. Beta blockers may also cause corneal hypoesthesia, impaired blinking and thus evaporation loss. Finally, vitamin A deficiency causes xerophthalmia, due to disorder of the goblet cells and mucin layer of tear film with the characteristic Bitot spot on the bulbar conjunctiva.^{4–8,18,21}

For a classification of dry eye on the basis of severity, the Delphi Panel Report was adopted and modified as a third component of the DEWS^{3,11} (see *Table 2*).

Clinical Approach Risk Factors

The prevalence of DED is higher in the presence of ocular conditions such as blepharitis, MGD and conjunctival disease. In clinical practice, the major

Table 2: Dry Eye Severity Levels (DEWS Criteria)^{3,11}

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity and frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+ /++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, decreased meniscus	Filamentary keratitis, mucus clumping, increased tear debris	Filamentary keratitis, mucus clumping, increased tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinisation, symblepharon
TBUT (seconds)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 minutes)	Variable	≤10	≤5	≤2

*Must have signs and symptoms. DEWS = International Dry Eye Workshop; MGD = meibomian gland disease; TBUT = tear break-up time.

risk factors for DED are age, female gender due to menopause hormones and reduced action of androgens (androgens are believed to be trophic for the lacrimal and meibomian glands), diabetes, thyroid disease, systemic medications especially antihistamines, anticholinergics, oestrogens, isotretinoin, selective serotonin receptor antagonists, amiodarone, glaucoma drops (beta blockers and preservatives), decreased corneal sensitivity (e.g. Herpes keratitis) and previous refractive corneal surgery.^{9,11-13}

Symptoms

Symptoms of DED vary in accordance to the underlying cause and the onset of the disease. Many patients present with a chronic burning sensation and blurred vision, associated with dryness, while others report tearing, which is a reflex due to the hyperactivation of the sensory sub-basal corneal nerve plexus.¹⁴ By contrast, reflex hyposalivation and a secondary tear film instability due to low blink rate might exist in patients with any kind of corneal neuropathy e.g. diabetes mellitus, thyroid disease and corneal surgery.^{9,14,15} In general, MGD (evaporative disorder) tends to be worse in the morning, and causes a foreign body sensation and sticky eyes, while the deficiency of tear production tends to be worse in the afternoon, or induces a continual irritation throughout the day. Itchy eyes and especially itchy, swollen eyelids and conjunctival papillae are usually related to ocular allergies.

Still, there is extensive changeability in patients' symptoms and clinical signs, and quite often this is related to the co-existence of several underlying causes of the multifactorial DED. Symptoms of dryness (which gets worse in environment with low humidity or in windy weather conditions), red eyes, foreign body sensation, grittiness, excessive tearing and light sensitivity are all potential complaints.

For the evaluation of symptoms, clinicians use one of the many available questionnaires, e.g. Schein's questionnaire or the more recent Ocular Surface Disease Index. However, there is not a universally accepted questionnaire. The questions explore the patient's symptoms within the space of one week, focusing on ocular irritation, functional symptoms and environmental conditions that trigger dry eyes. Higher scores indicate more severe disease.^{23,24}

Clinical Examination

Clinical examination should follow the recommendation of the DEWS for grading of severity of dry eye.

Examination should note any conjunctival injection/chemosis; also, examination of the lid margin should be performed to rule out meibomian gland disease.²⁵ Upper eyelid eversion to identify scarring or papillae that might be suggestive of inflammatory or allergic disease (e.g. atopic keratoconjunctivitis, vernal) is essential, especially in chronic disorders.

Corneal staining with fluorescein 2% is used to identify corneal epithelial punctate erosions and epithelial break-up areas. Marked central corneal staining is usually suggestive for dry eyes, and is also common in neurotrophic keratopathy. Upper 1/3 corneal staining is more commonly caused by vernal keratoconjunctivitis, superior limbic keratoconjunctivitis of Theodore and contact lenses. Lower 1/3 corneal staining might be secondary to eyelid malposition such as ectropion, lagophthalmos, rosacea, contact lenses or toxic epithelial reaction to ocular drops/preservatives. Other stains are the Rose Bengal, which stains mucin and epithelial necrotic cells, and Lissamine green, which is an alternative and causes less stinging. Both may reveal earlier and more subtle abnormalities, in comparison to fluorescein, but they are not popular due to their potential to cause ocular irritation.^{3,4,11,26}

Assessment of the tear meniscus – the tear layer between the lower eyelid and the globe, is important in the evaluation of DED and tear film disease. Tear meniscus should be approximately 0.5 mm to 1 mm in height. Reduced tear meniscus lower than 0.2 mm is suggestive for diminished tear production, while increased height suggests obstruction to the nasolacrimal system (punctal obstruction, canalicular stenosis or nasolacrimal duct obstruction).^{27,28} Also, the clinician could perform a dye disappearance test with a drop of 5 µl fluorescein placed in the inferior conjunctival fornix. The amount of fluorescein present in the tear lake is assessed after 5 minutes with a cobalt-blue light, and if most of the dye remains, the lacrimal system is unlikely to be functioning properly.⁵

Composition of tear meniscus is important as the presence of mild debris is a common clinical sign in cases of MGD and blepharitis. The co-existence of filamentary keratitis is even more suggestive for inflammatory DED. Careful examination of lid margin for meibomian gland disease should be performed and correlation with systematic disease, e.g. rosacea, should be considered. An early finding in patients with posterior blepharitis is hyperkeratinisation of the meibomian gland ductal epithelium. Loss of glandular architecture, dilation of the

ductules and ductal occlusion are also seen. Secretions from affected patients contain an increase in the concentration of free fatty acids, causing a direct toxic effect to the ocular surface and result in an impaired lipid layer and instability of the tear film.²⁵

TBUT should be performed to assess for instability of tear film and the evaporation component of DED. It is performed by instilling a drop of fluorescein in the lower fornix and asking the patient to blink and then keep the eyes open. TBUT is the time from the last blink to the development of the first dry spot in the central cornea, representing a deficiency on the tear film. A result of less than 10 seconds is considered abnormal, while 5 seconds or less is classified as stage four DED. Most experts repeat the test three times and calculate the mean outcome, thereby increasing the measurement's reliability and sensitivity.^{9,29}

Schirmer test is performed to investigate for tear deficiency DED. A strip of filter paper is inserted on the lateral third of the inferior lid margin, and the wetted paper is measured in millimeters after 5 minutes. Schirmer I, without anaesthetic drops, elicits basic and reflex tearing, and could be considered a valid option for severe DED where results can be reliably repeated.^{5,9} In mild or moderate disease, the measurement is not used alone, but it should be co-analysed with the other ocular surface findings, according to DWES. Measurement below 15 mm is considered moderately reduced, below 10 mm abnormal; if it is below 5 mm, then Sjögren's syndrome should be investigated further.^{16,17,19}

Corneal sensitivity should be measured at the central cornea, to identify cases of impaired sensory drive. A Cochet-Bonnet aesthesiometer (Luneau Ophthalmologie, Chartres, France), which is a nylon monofilament designed for corneal use, is applied 2 mm superior to the six o'clock limbal position in order to avoid the blink reflex. When the patient feels its presence, the length of the filament is recorded. The shorter the length indicates decreased sensation. The mean of three measurements it is best to use: values <4.0 cm are considered low.⁹

Non-invasive or minimally invasive tests provide more reproducible and objective data for the evaluation of the tear film. Meniscometry is particularly useful in assessing tear volume indirectly by measuring tear meniscus radius. A video-meniscometer, which enables calculation of the meniscus radius digitally, is useful for the diagnosis of tear-deficient dry eye. It also enables calculation of eye drop turnover revealing the need for punctal plugs and demonstrating dysfunction of the tear meniscus. Interferometry of the tear film lipid layer could be used in screening and evaluating dry eye severity and in selecting dry eye candidates for punctal occlusion. Meibometry is a minimally invasive technique to quantify the amount of meibomian lipid on the lid margin. Lipid is blotted onto a plastic tape and the change in optical density is used to calculate lipid uptake. Another technique for the assessment of MGD is laser meibometry. Also, the delivery of lipids from the lid reservoir to the precorneal tear film can be analysed using interferometry and laser meibometry.^{7,8,25,29}

However, one of the most significant measurements is the ocular osmolarity, according to a recent guideline of the American Academy of Ophthalmology Preferred Practice Patterns on Dry Eye Syndrome, it is noted that "tear osmolarity has been shown to be a more sensitive method of diagnosing and grading the severity of dry eye compared to corneal and conjunctival staining, TBUT, Schirmer test, and meibomian gland grading".^{29,30-32} In addition, tear osmolarity showed the lowest variability over time and the highest sensitivity to therapeutic intervention

compared with corneal staining, TBUT, Schirmer tests and meibomian gland grading.³³

A new biomarker test was recently approved by the FDA in December 2013 – the InflammDry (Rapid Pathogen Screening Inc.), which is a rapid in-office test for diagnosing DED. The test, which takes less than 2 minutes to perform, uses tear samples to detect the inflammatory marker MMP-9, which has been shown to be consistently elevated in the tears of patients with DED, due to the inflammation of the ocular surface.³⁴

Moreover, serology for circulating autoantibodies, including antinuclear antibodies (ANA), anti-Ro/SSA (common in patients with SLE), anti-La/SSB (more specific for primary Sjögren syndrome), anti-neutrophil cytoplasmic antibodies (ANCA), e.g. c-ANCA for Wegener, rheumatoid factor (Rf), thyroid-stimulating hormone (TSH), serum angiotensin-converting enzyme (ACE) for sarcoidosis, may be indicated according to history and systemic symptoms. Lacrimal gland or salivary gland biopsy may be performed to aid in diagnosing Sjögren syndrome.^{16,17,35}

Finally, impression cytology is a non-invasive technique that can replace conjunctival biopsy in confirmation of diagnosis in DED. One drop of local anaesthetic is instilled into the eye and a millipore cellulose acetate filter paper is applied on the conjunctiva or cornea or both together, straddling the limbus. The paper is allowed to remain in contact with the eye for approximately 5–10 seconds and then peeled off with forceps. Two or three superficial layers of the ocular surface epithelium are removed. Papanicolaou or haematoxylin and PAS are the commonly used stains and the fixating solution is usually ethyl alcohol and formaldehyde. In mucin layer deficiency, the epithelium may undergo squamous metaplasia, resulting in a loss of goblet cells and keratinisation. Specimens are graded as normal or abnormal based on epithelial cell morphology and goblet cell density. This method is very sensitive revealing conjunctival metaplasia and corneal limbal stem cell deficiency (an 80 % correlation was found between impression cytology diagnosis and histopathology specimens obtained from incisional biopsy). However, it requires proper staining and expert analysis of the specimen.^{8,25}

Management of Dry Eye Disease

Management of DED is related to its severity, according to DEWS classification. It is based on reducing the imbalance of tear production and evaporation (by improving tear film volume and stability and reducing tear evaporation and drainage), settling down the ocular surface inflammation and alleviating patient's symptoms. In all cases, control of the underlying systemic disease is needed in order to maintain control of DED (see *Table 3*).

At Level 1, the patient is advised on environmental modifications, e.g. to avoid prolonged activity that reduces blinking, such as prolonged reading or computer use, and to minimise exposure to air conditioning or heating. Humidifiers might be useful to maintain an acceptable humidity level that will keep the eyes moist and will reduce the evaporation of the tear film. Avoidance of hot, windy, low-humidity and high-altitude environments, as well as smog and smoke, is also advisable.^{36,37}

Artificial tears are considered as first-line treatment, as they normalise the tear film volume and also improve vision clarity. They should be used frequently, at least four times a day, to enable stabilisation of the ocular surface. Factors to consider when prescribing artificial tears are the viscosity, the preservatives and the substitutes. Low viscosity drops require more frequent administration, but they will not blur the

vision, in contrast to high viscosity drops, which have a prolonged effect but might cause blurred vision. Therefore, viscous paraffin-based ointments might be better administered only at night. Preservative-free drops are always better, as they do not exacerbate the inflammation in DED, but they are more expensive and this cost should be considered as the treatment is chronic.^{1,2,20}

As for the substitutes, hypromellose 0.3 % or polyvinyl alcohol drops are two of the simple lubricant drops that are popular for mild eye dryness. Carboxymethylcellulose 0.5 % in combination with the osmoprotective compatible osmolyte erythritol and glycerine is a more effective choice in providing cytoprotection and also osmoprotection simultaneously and thus requires less frequent use. This is comparable to the sodium hyaluronate 0.18 %, which is also cytoprotective and seems to have improved ocular surface retention to inflamed eyes, due to a specific binding to the CD44, a transmembrane cell surface adhesion molecule.³⁸

Lid hygiene is also advised as initial management of DED, when posterior blepharitis is an underlying causative factor. Warm compresses, lid massage and lid washing with a baby shampoo or soda solution will help empty the meibomian glands and improve secretion. Cases of anterior blepharitis, less common than posterior, are characterised by inflammation at the base of the eyelashes. In staphylococcal variants, fibrinous crusting around the eyelashes causes irritation, whereas in the seborrhoeic variant, dandruff-like skin changes around the base of the eyelids causes greasy scales around the eyelashes. Application of fusidic acid or chloramphenicol ointment on the eyelid margin might help control the disease. Also, topical azithromycin ophthalmic solution 1 % either tobramycin/dexamethasone ophthalmic suspension 0.3 %/0.05 % has been shown to improve meibomian gland secretion and improve both signs and symptoms of blepharitis.^{39,40} Tetracyclines e.g. doxycycline 100 mg are used for at least 4 weeks duration as they improve the meibomian gland disease and reduce the MMP-9 activity in tear samples.^{41,42} These measures reduce bacterial-induced changes in the lipid component of the tear film, which in turn reduces evaporative tear loss.

In cases of persisting DED, topical anti-inflammatories could be used to alleviate symptoms and treat the cycle of ocular inflammation. Short-term treatment with topical 1 % methylprednisolone not only improves clinical outcome, but a recent study has also demonstrated that it may decrease tear osmolarity and cytokine levels.⁴³ Cyclosporine 0.05 % is an immunosuppressive agent that has been found to reduce the ocular surface inflammation and improve DED. It is relatively safe but may need up to 6 weeks to have an effect. Combination treatment with topical 1 % methylprednisolone for the first few weeks provides faster symptom relief and improvement of ocular symptoms without serious complications.⁴³⁻⁴⁵

In more severe DED (stage 3), autologous serum (AS) can be derived from patients' blood and used for controlling the ocular inflammation. It contains growth factors, fibronectin, immunoglobulins and vitamins, usually at higher concentrations than in tears. In a recent study comparing different concentrations, 50 % AS with sodium hyaluronate was more effective than artificial tears in reducing symptoms, corneal epitheliopathy and promoting fast closure of corneal wounds in non-Sjögren patients, while in Sjögren patients 100 % serum was the more effective choice.^{46,47}

Exactly the optimal concentration of AS eye drops is not clearly known in the treatment of severe DED. An important component of AS eye drops which makes the dilution of AS to 20 % necessary is transforming growth factor beta (TGF-β). TGF-β is known to have an anti-proliferative

Table 3: Management of Dry Eye Disease

Level 1
Education and environmental/dietary modifications
Elimination of offending systemic medications
Preserved artificial tear substitutes, gels and ointments
Eyelid therapy
Level 2 – If Level 1 Treatment Is Inadequate, Add the Following:
Non-preserved artificial tear substitutes
Anti-inflammatory agents
Topical corticosteroids
Topical cyclosporine A
Topical/systemic omega-3 fatty acids
Tetracyclines (for meibomianitis, rosacea)
Punctal plugs (after control of inflammation)
Secretagogues
Moisture chamber spectacles
Level 3 - If Level 2 Treatment Is Inadequate, Add the Following:
Autologous serum
Contact lenses
Permanent punctal occlusion
Level 4 – If Level 3 Treatment is Inadequate, Add the Following:
Systemic anti-inflammatory agents
Surgery
Lid surgery
Tarsorrhaphy
Mucous membrane grafting
Salivary gland duct transposition
Amniotic membrane transplantation

effect and at high concentrations (approximately fivefold more in AS than tears) this molecule may suppress wound healing of the ocular surface epithelia. That is one of the reasons why 20 % dilution was used in a whole of the previous AS studies in the literature.^{46,47}

Punctal plugs may be used with caution in severe DED. Silicone or collagen plugs could be used initially for a trial period, and then a permanent punctal occlusion with cautery should be considered. Reported adverse effects in a systematic review included epiphora (overflow of tears), foreign body sensation, eye irritation and spontaneous plug loss. In cases of severe meibomian gland disease, punctal occlusion should be avoided, as it is likely to exacerbate the symptoms, due to inflammatory factors trapped in the water pool.^{48,49} By contrast, the results of a large prospective study shows that a dietary supplementation with a combination of omega-3 essential fatty acids (EFAs) and antioxidants is an effective treatment for dry eye, which might also be considered in meibomian gland disease.⁵⁰

Omega-3 and -6 are EFAs, (polyunsaturated fats). They are precursors of eicosanoids, which are locally acting hormones that mediate the inflammatory processes. The four main groups of eicosanoids are prostaglandins, prostacyclins, thromboxanes and leukotrienes. Omega-3 EFAs include alpha linoleic acid (AA) (flaxseed oil), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-6 EFAs include linoleic acid (LA), gamma-linoleic acid (GLA), dihomogamma-linoleic acid (DGLA) and arachidonic acid (AA).⁵¹

Evidence suggests that levels of omega-6 are sufficient in the Western diet, so that supplementation of omega-3 may be all that is required to improve the balance of EFAs and reduce inflammatory processes.⁵² Supplementation of omega-3 EFA demonstrates an anti-inflammatory action in the lacrimal gland: it prevents apoptosis of secretory epithelial

cells, increases tear secretion and improves meibomitis.^{53,54} The mechanism for this action appears to be through an increased production of the anti-inflammatory cytokines LTB3 and PGE3, which prevent the production of AA from DGLA.⁵⁰⁻⁵⁴ Therefore, a higher dietary intake of omega-3 fatty acids decreases the risk associated with dry eye symptoms.⁵⁰

Mucolytic drops of acetylcysteine 5 % are used in severe DED with corneal filaments, and secretagogues e.g. pilocarpine 2.5 mg tablets may be used in Sjögren syndrome with eye dryness and xerostomia; however, they have potential parasympathetic side effects.^{16,17} Systemic anti-inflammatory drugs to control an underlying systemic disease is best discussed with a physician. Soft bandage contact lens or therapeutic scleral lens could also suffice to re-establish corneal integrity in chronic filamentary keratitis or neurotrophic keratopathy.^{55,56} The main mechanism is the retention of a protective tear film layer between the corneal epithelium and contact lens.^{56,57}

Finally, surgical management of DED includes correction of eyelid malpositions, such as entropion or ectropion, and reduction of the palpebral aperture by the means of lateral or medial tarsorrhaphy, when more conservative measures have failed. Botulinum toxin injection on the upper eyelid or amniotic membrane transplantation could also protect the cornea and rescue an impending perforation in severe DED.^{27,28,49}

Conclusion

The authors have reviewed herein the clinical manifestation, differential diagnosis and managements options for DED, which tends to be common, chronic and interferes with the quality of life of patients, and is also a multifactorial disease. Due to complex aetiopathogenesis and the variety of signs and symptoms, correct diagnosis and treatment remain challenging. The use of DEWS definition for diagnosis and classification is helpful to categorise DED and to choose the most suitable treatment plan. ■

- Friedman NJ, Impact of dry eye disease and treatment on quality of life, *Curr Opin Ophthalmol*, 2010;21:310-16.
- Pflugfelder SC, Prevalence, burden, and pharmaco-economic of dry eye disease, *Am J Manag Care*, 2008;14(Suppl. 3):S102-6.
- The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007), *Ocul Surf*, 2007;5:75.
- The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Workshop (2007), *Ocul Surf*, 2007;5:93.
- Savini G, Prabhawasat P, Kojima T, et al., The challenge of dry eye diagnosis, *Clin Ophthalmol*, 2008;2:31-55.
- Foulks GN, Challenges and pitfalls in clinical trials of treatments to dry eye, *Ocul Surf*, 2003;1:20-30.
- Yokoi N, Komuro A, Non-invasive methods of assessing the tear film, *Experiment Eye Res*, 2004;78:399-407.
- Labbé A, Brignole-Baudouin F, Baudouin C, Ocular surface investigations in dry eye, *J Fr Ophthalmol*, 2007;30:76-97.
- Achtsidis V, Tentolouris N, Theodoropoulos S, et al., Dry eye in Graves' ophthalmopathy: correlation with corneal hypoesthesia, *Eur J Ophthalmol*, 2013;23:473-9.
- Gupta A, Sadeghi PB, Akpek EK, Occult thyroid eye disease in patients presenting with dry eye symptoms, *Am J Ophthalmol*, 2009;147:919-23.
- Behrens A, Doyle JJ, Stern L, et al., Dysfunctional tear syndrome: a Delphi approach to treatment recommendations, *Cornea*, 2006;25:900-7.
- Moss SE, Klein R, Klein BE, Prevalence of and risk factors for dry eye syndrome, *Arch Ophthalmol*, 2000;118:1264-8.
- Latkany R, Dry eyes: etiology and management, *Curr Opin Ophthalmol*, 2008;19:287.
- Belmonte C, Acosta MC, Gallar J, Neural basis of sensation in intact and injured corneas, *Exp Eye Res*, 2004;78:513.
- Zhang M, Chen J, Luo L, et al., Altered corneal nerves in aqueous tear deficiency viewed by *in vivo* confocal microscopy, *Cornea*, 2005;24:818-24.
- Fox RI, Stern M, Michelson P, Update in Sjögren syndrome, *Curr Opin Rheumatol*, 2000;12:391-8.
- Ramos-Casals M, Tzioufas AG, Font J, Primary Sjögren's syndrome: new clinical and therapeutic concepts, *Ann Rheum Dis*, 2005;64:347.
- Gilbard JP, Gray KL, Rossi SR, A proposed mechanism for increased tear-film osmolality in contact lens wearers, *Am J Ophthalmol*, 1986;102:505.
- Ramos-Remus C, Suarez-Almazor M, Russell AS, Low tear production in patients with diabetes mellitus is not due to Sjögren's syndrome, *Clin Exp Rheumatol*, 1994;12:375-80.
- Kaiserman I, Kaiserman N, Nakar S, Vinker S, Dry eye in diabetic patients, *Am J Ophthalmol*, 2005;139:498-503.
- Lemp MA, Crews LA, Bron AJ, et al., Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study, *Cornea*, 2012;31:472-8.
- Johnson ME, Murphy PJ, The effect of instilled fluorescein solution volume on the values and repeatability of TBUT measurements, *Cornea*, 2005;24:811-7.
- Bandeon-Roche K, Munoz B, Tielsch JM, et al., Self-reported assessment of dry eye in a population-based setting, *Invest Ophthalmol Vis Sci*, 1997;38:2469-75.
- Schiffman RM, Christianson MD, Jacobsen G, et al., Reliability and validity of the Ocular Surface Disease Index, *Arch Ophthalmol*, 2000;118:615-21.
- Foulks GN, Bron AJ, Meibomian Gland Dysfunction: a clinical scheme for description, diagnosis, classification, and grading, *Ocul Surf*, 2003;1:107-26.
- Nepp J, Abela C, Polzer I, et al., Is there a correlation between the severity of diabetic retinopathy and keratoconjunctivitis sicca?, *Cornea*, 2000;19:487-91.
- Kam KY, Cole CJ, Bunce C, et al., The lateral tarsal strip in ectropion surgery: is it effective when performed in isolation?, *Eye (Lond)*, 2012;26:827-32.
- Berry-Briccat A, Burns J, Sampath R, Inverting sutures for tarsal ectropion (the leicester modified suture technique), *Ophthalm Plast Reconstr Surg*, 2013;29:400-2.
- Lemp M, Sullivan B, Crews L, Biomarkers in dry eye disease, *European Ophthalmic Review*, 2012;6:157-63.
- Yokoi N, Komuro A, Maruyama K, et al., New instruments for dry eye diagnosis, *Semin Ophthalmol*, 2005;20:63-70.
- Khanal S, Millar TJ, Barriers to clinical uptake of tear osmolality measurements, *Br J Ophthalmol*, 2012;96:341-4.
- Preferred Practice Pattern Guidelines: Dry Eye Syndrome - Limited Revision, American Academy of Ophthalmology, San Francisco, CA, US, 2011.
- Sullivan BD, Crews LA, Messmer EM, et al., Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications, *Acta Ophthalmol*, 2014;92:161-6.
- Sambursky R, Davitt WF, Latkany R, et al., Sensitivity and specificity of a point-of-care matrix metalloproteinase 9 immunoassay for diagnosing inflammation related to dry eye, *JAMA Ophthalmol*, 2013;131:24-8.
- Mavragani CP, Skopouli FN, Moutsopoulos HM, Increased prevalence of antibodies to thyroid peroxidase in dry eyes and mouth syndrome or sicca asthenia polyalgia syndrome, *J Rheumatol*, 2009;36:1626-30.
- Abusharha AA, Pearce EI, The effect of low humidity on the human tear film, *Cornea*, 2013;32:429-34.
- Alex A, Edwards A, Hays JD, et al., Factors predicting the ocular surface response to desiccating environmental stress, *Invest Ophthalmol Vis Sci*, 2013;54:3325-32.
- Baudouin C, Cochener B, Pisella PJ, et al., Randomized, phase III study comparing osmoprotective carboxymethylcellulose with sodium hyaluronate in dry eye disease, *Eur J Ophthalmol*, 2012;22:751-61.
- Luchs J, Efficacy of topical azithromycin ophthalmic solution 1 % in the treatment of posterior blepharitis, *Adv Ther*, 2008;25:858.
- Torkildsen GL, Cockrum P, Meier E, et al., Evaluation of clinical efficacy and safety of tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% compared to azithromycin ophthalmic solution 1% in the treatment of moderate to severe acute blepharitis/blepharoconjunctivitis. *Curr Med Res Opin*, 2011;27:171.
- Frucht-Pery J, Sagi E, Hemo I, Ever-Hadani P, Efficacy of doxycycline and tetracycline in ocular rosacea, *Am J Ophthalmol*, 1993;15:116:88-92.
- Iovieno A, Lambiase A, Micera A, et al., *In vivo* characterization of doxycycline effects on tear metalloproteinases in patients with chronic blepharitis, *Eur J Ophthalmol*, 2009;19:708.
- Lee JH, Min K, Kim SK, et al., Inflammatory cytokine and osmolality changes in the tears of dry eye patients treated with topical 1% methylprednisolone, *Yonsei Med J*, 2014;55:203-8.
- Byun YJ, Kim TI, Kwon SM, Efficacy of combined 0.05 % cyclosporine and 1 % methylprednisolone treatment for chronic dry eye, *Cornea*, 2012;31:509-13.
- Kymionis GD, Bouzoukis DI, Diakonou VF, et al., Treatment of chronic dry eye: focus on cyclosporine, *Clin Ophthalmol*, 2008;2:829-36.
- Cho YK, Huang W, Kim GY, Lim BS, Comparison of autologous serum eye drops with different diluents, *Curr Eye Res*, 2013;38:9-17.
- Urzua CA, Vasquez DH, Huidobro A, et al., Randomized double-blind clinical trial of autologous serum versus artificial tears in dry eye syndrome, *Curr Eye Res*, 2012;37:684-8.
- Ervin AM, Wojciechowski R, Schein O, Punctal occlusion for dry eye syndrome, *Cochrane Database Syst Rev*, 2010;CD006775.
- Ohba E, Dogru M, Hosaka E, et al., Surgical punctal occlusion with a high heat-energy releasing cautery device for severe dry eye with recurrent punctal plug extrusion, *Am J Ophthalmol*, 2011;151:483-7.
- Oleñik A, Effectiveness and tolerability of dietary supplementation with a combination of omega-3 polyunsaturated fatty acids and antioxidants in the treatment of dry eye symptoms: results of a prospective study, *Clin Ophthalmol*, 2014;8:169-76.
- Rand AL, Asbell PA, Nutritional supplements for dry eye syndrome, *Curr Opin Ophthalmol*, 2011;22:279-82.
- Simopoulos AP, The importance of the ratio of omega-6/omega-3 essential fatty acids, *Biomed Pharmacother*, 2002;56:365-79.
- Rashid S, Jin Y, Ecoiffier T, et al., Topical omega-3 and omega-6 fatty acids for treatment of dry eye, *Arch Ophthalmol*, 2008;126:219-25.
- Roncone M, Bartlett H, Eperjesi F, Essential fatty acids for dry eye: A review, *Cont Lens Anterior Eye*, 2010;33:49-54.
- Grey F, Carley F, Biswas S, Scleral contact lens management of bilateral exposure and neurotrophic keratopathy, *Cont Lens Anterior Eye*, 2012;35:288-91.
- Albietz J, Sanfilippo P, Troutbeck R, Lenton LM, Management of filamentary keratitis associated with aqueous-deficient dry eye, *Optom Vis Sci*, 2003;80:420-30.
- McMonnies CW, Incomplete blinking: exposure keratopathy, lid wiper epitheliopathy, dry eye, refractive surgery, and dry contact lenses, *Cont Lens Anterior Eye*, 2007;30:37-51.