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Dry Eye: A Comprehensive Approach to Diagnosis and Management

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Dry eye, also termed keratoconjunctivitis sicca, is one of the commonest complaints presenting to an eye care practice and yet is rarely addressed with thorough examination and comprehensive treatment. It can be estimated that more than 500 000 Canadians suffer from dry eye. In the context of the rising prevalence and significant morbidity of dry eye disease, this issue of *Ophthalmology Scientific Update* describes the risk factors and etiopathology of dry eye disease. Methods of diagnosing and monitoring dry eye are outlined, and a basic treatment algorithm is provided.

Epidemiology

Depending on the criteria used to define the condition, the prevalence of dry eye varies between 5% and 30% in the population ≥50 years of age.[1] When epidemiological data from the largest dry eye studies to date, the Women's Health Study, and the Physicians' Health Study are extrapolated to the Canadian population, one may project that more than half a million Canadians suffer from dry eye.[2-5] In the Canada Dry Eye Epidemiology Study (CANDEES),[6] published in 1997, 28.7% of the 13 517 respondents reported symptoms of dry eyes, of whom 1.6% were categorized as "severe" and 7.8% were "constant but moderate". With the aging of the population, this number is rising and will place an increased burden on the healthcare system. Medicare data revealed a 57.4% increase in the incidence of dry eye from 1991 to 1998.[7] For comparison, the cataract case incidence increased 16.4% during this period.[7]

Although some complaints of dry eye can be relatively minor, others suffer significant morbidity. A subgroup study of the Women's Health Study and Physicians' Health Study found that patients with dry eye were 3 times more likely than age-matched controls to report difficulty with common activities such as driving, watching television, professional work, and computer work.[8] Schiffman et al[9] found that dry eye had a similar negative impact on quality of life as moderate angina.

Definition and Etiopathogenesis

The International Dry Eye WorkShop (DEWS) committee convened in 2007 to formulate a clear definition of dry eye based on a newer appreciation of the impact of inflammation and hyperosmolarity. The committee defined dry eye as a "multifactorial disease of the tears and ocular surface that results in significant 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] This definition takes into consideration the complexity of dry eye. It is not simply an imbalance between tear production and evaporation. Many other qualitative factors, such as tear distribution, mucin and lipid content, osmolarity, and concentration of inflammatory mediators, affect the ocular surface. The tear film is regulated by a complex interplay of main and accessory lacrimal glands and meibomian glands with the cornea and the eyelids. The tear film produces the most significant refractive interface of the eye; hence, patients experiencing tear-film dysfunction often complain of diminished vision that improves with blinking. Aside from its optical properties, the tear film is instrumental in maintaining eye health. When the tear film breaks down, resultant shear stress between lids and globe, hyperosmolarity, and increased inflammation stimulate nociceptive fibres in the cornea. The initial compensatory mechanism is reflex tear secretion. However, corneal sensation decreases with chronic inflammation, compromising the reflex response and further destabilizing the tear film in a perpetuating cycle.

Classification (Table 1)

The DEWS committee also developed a 3-part classification based on etiology, mechanisms, and disease stage.[10] Dry eye can be classified into 2 broad categories: aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE). Although it helps us understand the underlying pathogenesis, subclassification of dry eye into distinct categories is often an oversimplification. The categories are not mutually exclusive and patients typically have

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Table 1: Classification of dry eye dysfunction

Aqueous deficient dry eye (ADDE)

- Sjögren syndrome
  - Primary: no associated rheumatologic disease
  - Secondary: rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, Wegener granulomatosis, systemic sclerosis, primary biliary sclerosis, and mixed connective tissue disease
- Non-Sjögren syndrome
  - Lacrimal deficiency
  - Lacrimal gland duct obstruction
  - Reflex block
  - Systemic drugs

Evaporative dry eye (EDE)

- Intrinsic
  - Meibomian oil deficiency
  - Disorders of lid aperture
  - Low blink rate
  - Drug action
- Extrinsic
  - Vitamin A deficiency
  - Topical drugs and preservatives
  - Contact lens wear
  - Ocular surface disease (eg, allergy)

several types of dry eye that compound each other. This multifactorial etiology underlines the importance of addressing all aspects of dry eye with a comprehensive treatment protocol.

Aqueous deficient dry eye

ADDE refers to mechanisms that chiefly describe a failure in tear secretion. It can be divided into Sjögren syndrome and non-Sjögren syndrome dry eye, based on the nature of the inflammation. Inflammation limited to the ocular surface and lacrimal glands is termed non-Sjögren syndrome dry eye, whereas Sjögren syndrome dry eye is characterized by inflammation as part of a diffuse exocrinopathy affecting both salivary and lacrimal glands. ADDE can then be subclassified based on exact etiology. Lacrimal acinar destruction or dysfunction leads to decreased tear secretion. If tear production is sufficiently impaired or if there is a concomitant evaporative dry eye component, then tear film osmolarity increases. Although ocular surface inflammation initially promotes reflex tearing and compensation, it leads to deleterious effects through several mechanisms if left uncontrolled. A confocal microscopy study demonstrated morphological changes in the subbasal nerve plexus in patients with chronic inflammation and dry eye.[11] It is believed that these changes lead to the diminished corneal sensation that has been reported in numerous studies.[12-14] Some researchers even suggest that excessive reflex stimulation of the lacrimal glands can induce a neurogenic inflammatory cytokine response within the gland itself.[15,16] Inflammation leads to apoptotic cell death of epithelial cells, including goblet cells.[17] Reduction in goblet cells is a hallmark of all forms of dry eye. The resultant decrease in mucin production further destabilizes the tear film and aggravates dry eye.

Sjögren syndrome dry eye. An American-European consensus group[18] revised specific criteria for diagnosis of Sjögren syndrome to include the following: objective signs of ADDE on examination, symptoms of dry eye and dry mouth, presence of serum autoantibodies to Ro(SSA) or La(SSB), evidence of salivary gland impairment on functional tests, and histopathological confirmation of lymphocytic infiltration of the salivary glands. The underlying pathogenesis of the exocrine dysfunction that characterizes this disorder is T cell-mediated inflammation that destroys the acinae and ductules of both lacrimal and salivary glands. Sjögren syndrome dry eye can be further subclassified as either primary or secondary depending on whether it is associated with an underlying autoimmune disorder. In practice, functional tests and salivary gland biopsies confirming true Sjögren syndrome are rarely done. However, when Sjögren syndrome is suspected, referral to a rheumatologist should be initiated as the identification of an underlying autoimmune disorder may direct treatment of both the Sjögren syndrome as well as the underlying systemic condition.

Non-Sjögren syndrome dry eye. The incidence of dry eye increases with age presumably because of associated increases in ductal pathology, acinar cell atrophy, and lymphocytic glandular infiltration. This age-related dry eye is a relatively common entity that some believe may be caused by chronic low-lying dacryoadenitis or subclinical conjunctivitis. Lacrimal gland deficiency may also be caused by infiltrative disease such as sarcoidosis, lymphoma, and graft-versus-host disease. The lacrimal ducts themselves can be obstructed by cicatrizing processes such as trachoma, cicatricial pemphigoid, erythema multiforme (Stevens Johnson syndrome), and chemical and thermal burns. Since afferent feedback from the cornea stimulates tear production, any condition that decreases corneal sensation impairs tear production. Common examples include diabetes, neurotrophic keratitis, contact lens wear, refractive surgery, and topical anesthesia. Damage to the efferent nerves, particularly cranial nerve VII and its ocular branch nervus intermedius can cause dry eye by reducing secretomotor function. More common causes of secretomotor dysfunction include systemic drugs such as antihistamines, beta-blockers, antispasmodics, diuretics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and other psychotropic drugs.

Evaporative dry eye

EDE refers to conditions that impair retention of a uniform tear film on the ocular surface, even in the presence of normal tear production. EDE can be subclassified into 2 broad categories: intrinsic and extrinsic.

Intrinsic EDE refers to pathology that is dependent on conditions that arise on the eyelids and ocular surface, such as meibomian oil deficiency and surface exposure. Meibomian gland dysfunction (MGD), a term that has incorrectly been used interchangeably with posterior blepharitis, is by far the most common form of EDE. It has also been recognized to play a contributory role in many forms of ADDE. Population based studies have reported MGD prevalences from 3.5% to as high as 70%.[19-25] An International Workshop on MGD, involving 50 experts from around the world, defined MGD as "(a) chronic diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualita-

tive/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease."[19]

MGD can be further subclassified into low- and high-delivery states. In turn, there are 2 categories of low-delivery states: hyposecretory and obstructive. Hyposecretion may result from primary gland atrophy, but may also occur as a result of contact lens wear or use of systemic drugs such as retinoids. Meibomian gland obstruction is the most common cause of MGD. Hypertrophy of the duct epithelium and keratinization of the orifices lead to blockage of terminal ducts. This obstruction is commonly seen in older subjects and has been linked to reduced androgen levels.[26] Numerous systemic factors have been associated with hyposecretion or blockage of the meibomian glands; eg, rosacea, seborrheic dermatitis, atopic dermatitis, and psoriasis. MGD, especially if associated with rosacea, is associated with increased numbers of commensal lid margin flora. *Staphylococcus epidermis*, *Staphylococcus aureus*, and *Propionibacterium acnes* destabilize the tear film by releasing lipases that break down the cholesterol esters in meibum. These lipases and free fatty acids form an irritating "meibomian foam" that causes ocular surface inflammation, thus contributing to the inflammatory pathogenesis of dry eye. Additionally, studies have demonstrated that meibum secretions rich in cholesterol facilitate growth of staphylococcal strains on the lid margin. Cicatricial disease blocks lacrimal ducts but can also block meibomian gland orifices, resulting in mixed ADDE and EDE. Although not classically considered a cicatricial disorder, chronic rosacea blepharitis may lead to cicatricial changes of the meibomian glands. In cicatricial MGD, the gland orifices are drawn backward against the globe and are unable to effectively deliver their secretions to the ocular surface. Atopy, ocular cicatricial pemphigoid, erythema multiforme, and trachoma are examples of diseases that cause cicatricial MGD.

High-delivery states of MGD are usually associated with acne. Conditions such as seborrheic dermatitis and acne rosacea increase sebum production and also lead to hypersecretion of meibum from the meibomian glands. Although tear film dysfunction is more commonly a result of oil hyposecretion, hypersecretion can also destabilize the lipid layer.

Any condition that increases the exposed surface area of the eye or the duration of exposure can cause EDE. Even variations of normal physiology and activity such as high myopia and activities with prolonged upgaze can contribute to exposure.

Extrinsic causes such as diet, allergic eye disease, topical medications, contact lens wear, and refractive surgery can induce EDE. Exposure to antigens in ocular allergic disease leads to degranulation of immunoglobulin E-primed mast cells and inflammatory cytokines. Surface epithelial death in both the cornea and conjunctiva further perpetuate inflammation and tear dysfunction. Although antihistamines treat ocular allergies, they may worsen dry eye by reducing aqueous secretion. Benzalkonium chloride (BAK), a preservative found in many topical medications, can interfere with surface wettability and cause surface epithelial cell damage and punctate epithelial keratitis. Preservatives in glaucoma medications are a common cause of EDE and may be improved with switching to nonpreserved formulations. All types of soft contact lens materials increase the evaporation rate and decrease the tear film break-up time. About 50% of contact lens wearers report dry eye and are 12 times more likely to report dry eye as compared to emmetropes.[27,28] Refractive surgery, particularly laser-assisted *in situ* keratomileusis (LASIK), is a known cause of dry eye and has been reported in 0.25% to 48% of cases.[29,30] The transection of corneal nerves reduces corneal sensation secondarily resulting in decreased blink rate and reduced lacrimal secretion. Some authors postulate that trophic sensory support is disrupted to the denervated area, and have termed the condition LASIK-induced neuroepitheliopathy (LINE).[31] The rate of dry eye is highest immediately post surgery, decreasing to 33.36% at 6 months, and returning to baseline at 1 year according to most studies.[1]

Risk Factors of Dry Eye

The DEWS committee identified definitive and suggestive risk factors for dry eye.[1] Most common well-substantiated risk factors include older age, female sex, postmenopausal estrogen therapy, and a diet low in Ω-3 essential fatty acids. Sex steroid deficiency has been associated with dry eye in several conditions such as androgen insufficiency syndrome, Sjögren syndrome, and antiandrogen medication treatment. Progressive diminution in circulating androgens may also be an underlying precipitant for age-related dry eye.[32] A large-scale study by Schaumberg et al[33] of more than 25 000 women found that postmenopausal estrogen therapy increased the risk of dry eye. When estrogen was combined with progesterone the risk increased mildly from 5.9% to 6.7%. When estrogen was taken by itself, however, the risk of dry eye increased to 9.0%. Large-scale epidemiological studies have also shown that diets low in Ω-3 fatty acids are associated with dry eye.[34,35]

Diagnosis

There is no gold standard for the diagnosis of dry eye; the patient's symptoms, medical history, slit lamp examination, and diagnostic tests must all be considered. Questionnaires are invaluable tools that can be used in a clinical setting both to diagnose ocular surface disease and to monitor the efficacy of treatment. Numerous questionnaires have been introduced; many are designed as research tools and are not well suited for the fast pace of a clinical environment. In a Canadian Consensus paper,[36] Dr. Bruce Jackson introduced the Canadian Dry Eye Assessment (CDEA) questionnaire, a modification of the Ocular Surface Disease Index questionnaire (Figure 1). The CDEA questionnaire is a powerful tool as it quantifies the severity of ocular surface disease and provides a treatment algorithm based on results of the questionnaire (Figure 2). The clinical examination should be performed in a specific sequence and is modified depending on severity (Table 2).

With a slit lamp examination, the tear meniscus is examined paying particular attention for debris. The tear film break up time (TBUT) is then used to assess the quality of the tear film. After about 2 minutes, the staining on both the cornea and the conjunctiva are graded. Conjunctival staining may take longer to present. If there is moderate to severe corneal staining and a decreased tear meniscus, a Schirmer test is conducted to determine aqueous output. Finally, the lids are examined for signs of MGD and the glands are expressed with digital pressure over the eyelids. Particular attention is paid to the volume and quality of meibum.

Specialized dry eye clinics may improve the accuracy of diagnosing dry eye by sampling the tear film to measure osmolarity and inflammatory markers.[37] Ideally, these tests should be performed at the onset of the examination before reflex tearing is stimulated or any drops are placed in the eye. Osmolarity testing is commercially available in Canada; matrix metalloproteinase 9 has just been approved in Canada but as of this publication is not yet commercially available.

Treatment

Treatment should be implemented in a gradual, stepwise manner, escalating from conservative lifestyle modifications to medical treatment, and then to surgical management and assistive devices. However, in severe disease, a comprehensive multifaceted treatment approach may be instituted at the outset.

Lifestyle modifications include methods such as decreasing work that requires prolonged attention (eg, computer work), increasing active blinking during these tasks, lowering the height of video display terminals to decrease upgaze-related exposure, increasing humidification, avoidance of cigarette smoke, and using moisture-retaining goggles.

Lid hygiene and warm compresses

If done properly, lid hygiene and warm compresses are among the most effective for dry eye disease. They are particularly useful in the MGD form of evaporative dry eye; however, given the safety of these conservative treatments and the frequent contribution of MGD to other forms of ADDE, these treatments can be recommended to most patients with dry eye. Some authors suggest that MGD may cause a shift towards a higher melting point of meibomian secretions. Hot compresses improve flow by breaking down pathologically altered meibum. Olson et al[38] reported that 5 minutes of warm towel compress (40°C) increased tear film lipid layer thickness by 80%. Compliance with warm compresses, however, can be hindered by impractical recommendations of frequent application and by improper technique and perceived inefficacy. Compliance is often maximized when it is incorporated into the patient's routine, such as use of a wet facecloth in the shower. Optimally, these compresses are combined with meibomian expression through firm massage of the eyelids.

Periodic use of commercial eyelid cleaners may help remove debris from obstructed meibomian glands but should not be overused as it may cause irritation. Thermal pulsation devices are commercially available in Canada. These cupping devices provide direct massage and heat to the eyelids, and have been shown to be efficacious; however, the high cost may be prohibitive to many patients.

Artificial tears

A large number of tear supplements exist on the market that vary depending on the active ingredient, electrolyte composition, surfactant and viscosity. "Artificial tear" is a misnomer, as no tear supplement can replace the complexity of the human tear. Artificial tears act primarily as lubricants; however, their efficacy in relieving patient symptoms cannot be attributed solely to their volume effect. Using optical coherence tomography imaging of the tear meniscus, our group demonstrated that tear volume returned to baseline just

Figure 1: Canadian Dry Eye Assessment (CDEA)

Patient ID: _____ Date: _____

Please complete this questionnaire. It will help to grade the severity of your Dry Eye symptoms.

	0	1	2	3	4	
Have you experienced any of the following symptoms?	None of the time	Some of the time	Half of the time	Most of the time	All of the time	Scoring 0–4
1. Sensitivity to light, during the last week						
2. Gritty or scratchy sensation, during the last week						
3. Burning or stinging, during the last week						
4. Blurred/unclear vision, during the last week						
5. Vision that fluctuates with blinking, during the last week						
6. Vision that improves with artificial tears, during the last week						
7. Tearing/watering, during the last week						
8. Pain/burning during the night or upon awakening in the morning, during the last week						
Have you experienced eye irritation while performing any of these activities?						
9. Reading or driving a car for long periods, during the last week						
10. Watching TV/working on a computer for an extended period, during the last week						
Have your eyes felt uncomfortable in any of the following situations?						
11. During wind/air draft exposure, during the last week						
12. In places with low humidity (heated/cooled places, i.e. planes), during the last week						
						TOTAL SCORE
How much do your eyes bother you? Please check box from 1 – 10					TOTAL SCORE: Add scores from questions 1 - 12	

1 Not at all	2	3	4	5 Moderately	6	7	8	9	10 Extremely & constantly
○	○	○	○	○	○	○	○	○	○

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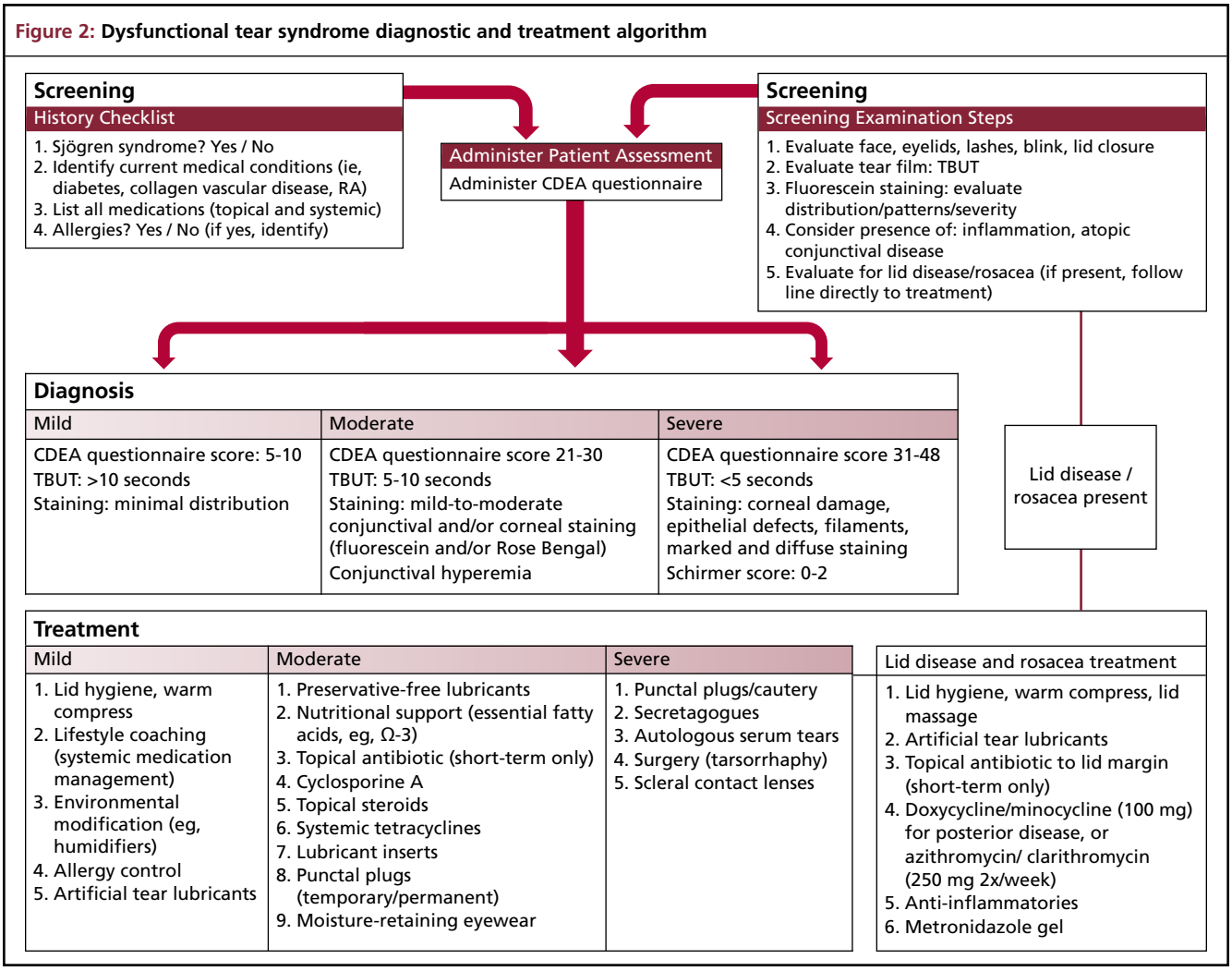
Figure 2: Dysfunctional tear syndrome diagnostic and treatment algorithm



10 minutes after instillation of carboxymethylcellulose tear supplements.[39] Despite the transient volume effect of artificial tears, patients continue to have prolonged (albeit rarely complete) relief of symptoms. The introduction of new formulations with lipid components may have promise in patients with MGD. Tear retention time increases with increased viscosity from liquids to gels to ointments; however, as viscosity increases so does the blurring effect of the tear supplement, thus limiting the use of high-viscosity agents such as ointments to predominantly nighttime application.

Frequent use of ocular lubricants may have deleterious effects as it may wash out favourable trophic elements and if preserved may instigate further ocular inflammation. Preservatives such as BAK and ethylenediamine tetra-acetic acid (EDTA) may add to the toxicity of eye drops and cause ocular surface disease.[40] It is well tolerated if used less than 4-6 times per day by patients with mild dry eye; however, patients with moderate or severe dry eye who apply more frequently should consider a preservative-free supplement or formulations with preservatives that are less toxic (eg, polyquaternium-1) or transient (eg, sodium perborate and sodium hypochlorite). Sodium perborate converts into water and oxygen upon contact with the tear film, while hypochlorite degrades into chloride ions and water with UV exposure. These preparations are less toxic but may still cause ocular irritation when they do not fully degrade in patients with significant dry eye and limited tear volume. Ointments do not support bacterial growth, and generally do not contain preservatives; however, some contain parabens or lanolin, which may cause irritation in patients with dry eye.

Topical antibiotics

There is a paucity of controlled peer-reviewed studies demonstrating definitive efficacy of topical antibiotics in the treatment of MGD and dry eye. However, numerous clinical findings and the presence of excessive bacterial colonization in MGD suggest causality. When dry eye is associated with blepharitis, it is reasonable to use antibiotics in a pulse manner to decrease bacterial load. Typically an antibiotic ointment or gel is used 1-2 times daily for 1-2 weeks. Common ointment preparations include bacitracin, fusidic acid, ciprofloxacin, and erythromycin. There is some

Table 2: Diagnostic tests used in the investigation of ocular surface disease

Examination	Technique	Comments
Slit-lamp examination	Examine the tear meniscus, look for epithelial cell debris	Inferior shortening of the fornix indicates scarring
TBUT	Perform prior to instilling drops or manipulating the lids Instill 1-5 µL of fluorescein in preservative-free saline into the inferior cul-de-sac or moisten a fluorescein strip Instruct the patient to stare straight ahead and not blink TBUT is the interval between a blink and the development of the first discontinuity in the fluorescein-stained tear film	Provides an estimate of tear film stability Abnormal is <10 seconds A rapid TBUT may be due to aqueous tear deficiency, but is more typical of meibomian gland or goblet cell problems
Surface dye staining	Fluorescein: instill saline and apply strips or use a 1%–2% solution Observe with a cobalt blue filter and grade severity	Provides an estimate of damage Staining is more easily visualized on the cornea than the conjunctiva Reveals epithelial barrier disruptions and desquamation of superficial cells Disruption of intercellular junctions allows penetration of dye into the underlying tissue
	Rose bengal or lissamine green:* apply a saline-moistened strip or instill a 1% solution Observe with a red-free filter and grade severity	Provides an estimate of damage Stains conjunctiva more intensely than cornea Stains dead and devitalized cells and epithelial cells that are inadequately coated with tears, particularly mucin Lissamine green has similar properties to rose bengal, but is less irritating and is preferred by many ophthalmologists*
Schirmer test	Blot the eyes to remove excess tears Place Whatman #41 filter paper strips at the junction of the middle and lateral thirds of the inferior fornix and wait 5 minutes The eyes are closed to limit the effect of blinking	Provides an estimate of tear flow There is wide day-to-day variability; thus, an isolated abnormal result can be misleading but serially consistent results are highly suggestive
	Basic secretion test Is conducted with topical anesthesia	≤5 mm of wetting is abnormal >5–10 mm of wetting is equivocal >10 mm of wetting is normal
	Schirmer I Same as the basic secretion test without anesthesia	Measures basic and reflex secretion <10–15 mm of wetting is abnormal
	Schirmer II Same as Schirmer I with irritation of the nasal mucosa by a cotton applicator	Measures reflex secretion <15 mm of wetting is abnormal

*Leiter's Rx Ophthalmic Compounding, San Jose, Calif. TBUT = tear film break-up time.

concern that some bacterial flora have developed resistance to erythromycin. A newer-generation macrolide, azithromycin, has been developed with better coverage. Furthermore, there is evidence to suggest that azithromycin has additional immunomodulatory and anti-inflammatory effects.

Anti-inflammatory therapy

With the recognition of dry eye as an inflammatory disease, there has been a paradigm shift in management. Three classes of anti-inflammatory agents have demonstrated both experimental and clinical efficacy in treating dry eye and now have a place in the treatment algorithm when dry eye is uncontrolled by artificial tears and lifestyle modification.

Corticosteroids. Level 1 evidence demonstrates the benefit of several corticosteroid preparations, including methylprednisolone followed 2 weeks later by punctal occlusion,[41] loteprednol etabonate 0.5% ophthalmic suspension,[42] and fluoromethalone combined with artificial tears.[43] Although efficacious, steroid use is not without risk and thus should not be used long-term in the management of dry eye. Due to their rapid onset of action, corticosteroids are ideally used as a pulse therapy.

Cyclosporin A has emerged as a potent and safe treatment for dry eye. It decreases inflammation by inhibiting activation of T lymphocytes. Since it does not have any effect on already activated T lymphocytes, patients may not experience improvement until 4-6 weeks after initiation of therapy and thus must be counselled

accordingly to ensure compliance. Two trials of 877 combined patients showed significant improvement in subjective symptoms and objective findings such as corneal staining and Schirmer test (with anesthesia).[44] Goblet cell density increased by approximately 200% in treated eyes. Both doses (0.05% or 0.1% twice daily) had an excellent safety profile and no systemic cyclosporin was detected in the patients' blood with 12 months of use.

Tetracyclines and their analogues (eg, doxycycline, minocycline) improve dry eye disease by 3 potential mechanisms: antimicrobial, anti-inflammatory, and antiangiogenic. With a reduction of bacterial flora, there is a concomitant reduction in lipase production and proinflammatory meibomian lipid breakdown products.[45,46] Not only do they decrease bacterial concentrations but they also directly inhibit bacterial lipase activity. Other intrinsic anti-inflammatory properties include the suppression of numerous inflammatory factors such as collagenase, phospholipase A2, matrix metalloproteinase's, interleukin 1 and tumour necrosis factor. There is some experimental evidence suggesting that minocycline and doxycycline may inhibit angiogenesis in the cornea. This may explain their particular efficacy in treating rosacea blepharitis. The tetracycline derivatives, doxycycline and particularly minocycline, are lipophilic and therefore have greater concentration in the tears as compared to their tetracycline progenitors. Both doxycycline and minocycline can be used at 100 mg bid for 2 weeks then daily for 3 months. Recent studies suggest that doses as low as 40 mg may be sufficient as maintenance therapy. If the patient cannot tolerate tetracyclines, 250 mg of azithromycin or clarithromycin can be administered twice weekly.

Ω-3 fatty acids

Essential fatty acids such as Ω-3 and Ω-6 fatty acids play important roles in mediating inflammation. Ω-6 fatty acids are broken down to arachidonic acid and other pro-inflammatory mediators; in contrast, Ω-3 fatty acids block the synthesis of these lipid mediators, thus exerting an anti-inflammatory effect. Unfortunately the typical North American diet consists of 20-25 times more Ω-6 fatty acids than Ω-3. A diet rich in Ω-3 fatty acids can be obtained by eating flax seed oil and fish oils; however, to reach the recommended daily dose of 2000-3000 mg, a person would have to eat a serving of salmon every day. Thus, vitamin supplementation is advised in significant dry eye. When prescribing high-dose essential fatty acids, the clinician should be cognizant of their anticoagulant properties.

Punctal occlusion

The beneficial effect of punctal occlusion in dry eye has been documented in a number of studies.[47,48] Improved corneal staining, prolonged tear film break up time, decreased tear osmolarity, and increased goblet cell density have been demonstrated. Symptomatic improvement was reported in 74%-86% of patients. The CDEA[36] recommend punctal occlusion in patients with moderate to severe dry eye. More specifically, a review on punctal plugs recommended their use in symptomatic patients with ocular surface staining and <5 mm of tear strip wetting on a Schirmer basic secretion test (with anesthesia). Punctal occlusion should be avoided in dry eye patients with significant ocular inflammation, as it may prolong retention of pro-inflammatory cytokines. It is prudent to treat concomitant blepharitis prior to implementing occlusion. Prior to plug insertion, perform nasolacrimal duct irrigation to ascertain whether their placement will provide any benefit. The most common complication is extrusion of the plug;[49] there have also been reports of internal migration of the implant, infection, biofilm formation, and pyogenic granulomas.

Secretagogues

The muscarinic agonist pilocarpine has been shown to improve tear and saliva production in patients with Sjögren syndrome.[50] While pilocarpine appears to be more efficacious in treating the dry mouth, patients also reported improvement in dry eye symptoms. An increase in goblet cell density has been observed after 1-2 months of therapy. The most significant limitation of pilocarpine is its systemic cholinergic adverse effects: 40% of subjects receiving oral pilocarpine 5 mg qid reported excessive sweating, and chill (20%), nausea (13%), oversalivation (13%), and intestinal cramping (7%) were also reported. Cevimeline is another oral cholinergic agent that may be associated with fewer adverse systemic side effects at the treatment dose of 15-30 mg tid.

Autologous serum tear substitute

Autologous serum can be isolated by centrifuging the patient's own venous blood. It is stored in nonpreserved vials at concentrations ranging from 20%-100%. However, this is a laborious process that needs to be repeated frequently as the nonpreserved serum cannot be stored for extended periods due to sterility concerns. Because of these practical limitations, use of autologous serum has been reserved for severe cases of dry eye disease, in which it is associated with marked improvement.

Contact lenses

Hydrophilic bandage contact lenses may be helpful in certain cases of mild dry eye and those with secondary epithelial defects. The contact lens enhances lubrication by providing a reservoir of fluid and facilitates healing by providing a barrier against the shearing forces of the eyelids. However, in moderate to severe cases, lubrication may be inadequate to allow movement of the soft contact lens. In this case, the resultant hypoxia and irritation can worsen the inflammation and predispose the patient to infection and vascularization. Some scleral contact lenses, on the other hand, are specifically designed to vault over the cornea and provide a full fluid reservoir. The initial fitting and associated costs may be prohibitive to some patients. Once fitted, however, most patients experience marked improvement in vision and comfort even with recalcitrant dry eye disease.

Surgical procedures

The vast majority of patients will respond to the aforementioned interventions. Recalcitrant cases of dry eye may, however, require surgical management. Tarsorrhaphy is very effective in managing dry eye that has not responded to other treatments, particularly if there is a cause for exposure keratopathy. Horizontal lid-tightening procedures may improve the quality of the blink and thus facilitate meibomian gland expression.

Alternative, rarely performed procedures include: Gunderson conjunctival flap, amniotic membrane transplant, and salivary gland autotransplant.

Conclusion

Dry eye, or dysfunctional tear syndrome, is a common disease with significant morbidity and an increased prevalence in our aging population. It is a complex disease with many contributing factors. As such it requires a comprehensive approach to both evaluation and management. Regardless of etiology, a multi-tiered approach can be used to satisfactorily treat the vast majority of dry eye patients. Along with our improved understanding of the pathogenic role of hypersomolarity and inflammation in dry eye, several effective treatments have been added to our armamentarium. With continued research interest and development of new technologies, our already effective treatment protocol promises to experience continued refinement and improvement in the near future.

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