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Dry Eye Syndrome

According to the International Dry Eye Workshop (DEWS), ***dry eye is 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].

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

DEWS further defined that dry eye is the result of a breakdown or disturbance of the Lacrimal Functional Unit (LFU) that consists of the interaction between:

- Lacrimal glands
- Ocular surface
 - Cornea
 - Conjunctiva
 - Meibomian glands
- Eyelids
- Sensory and motor nerves – from the ocular surface as well as the nasal mucosa

Conditions impacting or damaging any of the above components can lead to tear film destabilization and dry eye (ocular surface disease). Tear film instability occurs when there is:

- Decreased tear secretion
- Delayed tear clearance
- Altered tear composition

The effects of tear film instability result in:

- Secondary ocular surface inflammation
 - Increased reflex tear secretion (initially)
 - Prolonged inflammation leads to chronic secretory dysfunction as well as reduced corneal sensation
 - Reduced reflex tear secretion (long term)
 - Worse tear film stability

Aqueous Tear-Deficient Dry Eye (ADDE)

ADDE or keratoconjunctivitis sicca (KCS) occurs from a reduction of the watery portion of tear secretion from the lacrimal gland. This reduction in tear secretion is typically a result of lacrimal gland acinar destruction or dysfunction [2] [3]. A lower aqueous component of the tears results in an increase tear

osmolarity which leads to a cascade of ocular surface inflammation. The resulting inflammatory mediators found in this situation include:

- Interleukins
- Tumor necrosis factor- α
- **Matrix metalloproteinases (MMP-9)**

While we have clinical tools to help us determine if there is inflammation on the surface of the eye, we can't know for sure if the inflammation on the ocular surface is a result of lacrimal gland inflammation or from inflammation from the ocular surface itself.

We can classify ADDE into Sjogren Syndrome Dry Eye and Non-Sjogren Syndrome Dry Eye

Sjogren Syndrome Dry Eye (SSDE)

SSDE is an autoimmune condition that results in T-cell infiltration of the salivary and lacrimal glands which leads to hyposecretion secondary to acinar and ductular cell death [4]. Patients with SSDE also have a higher frequency of Meibomian gland dysfunction than the general population [5]. SSDE can be categorized as:

1. Primary Sjogren consists of [6]:
 - a. ADDE
 - b. Dry mouth with signs of reduced salivary gland secretion
 - c. Auto-antibodies
 - d. Positive focus score on minor salivary gland biopsy
2. Secondary Sjogren includes the clinical picture of Primary Sjogren AND connective autoimmune disease including [1]:
 - a. Systemic Lupus Erythematosus
 - b. Polyarteritis nodosa
 - c. Wegener's granulomatosis
 - d. Systemic sclerosis
 - e. Primary biliary sclerosis

SS Association

Non-Hodgkin lymphoma (NHL) occurs at a greater rate in patients with connective tissue diseases. Additionally, patients with Primary Sjogren Syndrome have an elevated risk of B-cell lymphoma and other non hematological cancers such as thyroid, oral and stomach [20].

Non-Sjogren Dry Eye (NSDE)

NSDE occurs when reduced lacrimal function occurs in the absence of Sjogren Syndrome. NSDE can be broken down into multiple conditions that contribute to lacrimal deficiency. These include [1]:

1. **Primary lacrimal gland deficiencies** occur when the initiating factor in dry eye results from a reduction in the lacrimal gland function.
 - a. Age-related dry eye
 - b. Congenital alacrima
 - c. Familial dysautonomia
2. **Secondary lacrimal gland deficiencies** occur when the initiating factor in dry eye is another condition that causes damage to the lacrimal gland resulting in a reduction in lacrimation. Most of these below are secondary to inflammation that damages the lacrimal gland.

- a. Lacrimal gland infiltration
 - b. Sarcoidosis
 - c. Lymphoma
 - d. AIDS
 - e. Graft vs host disease
 - f. Lacrimal gland ablation
 - g. Lacrimal gland denervation
3. **Obstruction of the lacrimal gland ducts** occurs when conditions that cause scarring or cicatrization of the ocular surface leads to blockage of main and accessory lacrimal glands. This scarring can further impact the Meibomian glands as well as the eyelid anatomy that results in poor tear film distribution across the ocular surface.
- a. Trachoma
 - b. Cicatricial and mucous membrane pemphigoid
 - c. Erythema multiforme
 - d. Chemical and thermal burns
4. **Reflex hyposcretion** occurs when there is a decrease in the reflex sensation of the ocular surface when the eyes are open and also a reduced blink rate which increases evaporative stress of the ocular surface.
- a. Reflex sensory block
 - i. Contact lens wear
 - ii. Diabetes Neurotrophic keratitis
 - b. Reflex motor block
 - i. CN VII damage
 - ii. Multiple neuromatosis
 - iii. Exposure to systemic drugs

Normal Reflex

When we are awake, the trigeminal nerve (V2) feels the eye and senses reduction in tear volume. Through this sensation variations in the ocular surface can result in a normal upregulation of aqueous tear production to compensate for changes in that occur on the ocular surface. Examples of this would include increased evaporative stress and foreign body sensation.

Evaporative Dry Eye

Evaporative dry eye is a result of excessive aqueous water loss that occurs to the ocular surface when there is still normal function of the lacrimal glands. These have been classified into intrinsic and extrinsic contributors [1].

1. **Intrinsic factors** impacting the eyelid function and eyelid structures include:
 - a. Meibomian gland dysfunction
 - b. Disorders of lid/globe apposition
 - i. Entropion
 - ii. Ectropion
 - iii. Ptosis
 - iv. Blepharoplasty
 - c. Reduced blink rate
2. **Extrinsic factors** occur when the increased evaporation of the ocular surface occurs from some external source, these include:

- a. **Ocular surface disorders** which lead to poor wetting of the ocular surface or increased tear break up
 - i. Vitamin A deficiency
 - ii. Topical medications and preservatives
- b. Contact lens wear causes a splitting of the tear film into pre-lens and post-lens and results in lower tear volume on the ocular surface which can lead to destabilization.
- c. Ocular surface disease that results in loss of goblet cell function, these are covered above.
- d. Allergic conjunctivitis

Epidemiology

It is estimated that dry eye impacts [1]:

- 4.91 million Americans 50 years and older
 - 3.23 million women
 - 1.68 million men
- Tens of millions more have more mild episodic signs and symptoms

The prevalence of dry eye appears to be between 5-35% depending on age and may be more prevalent in Hispanic and Asian women [7] [8].

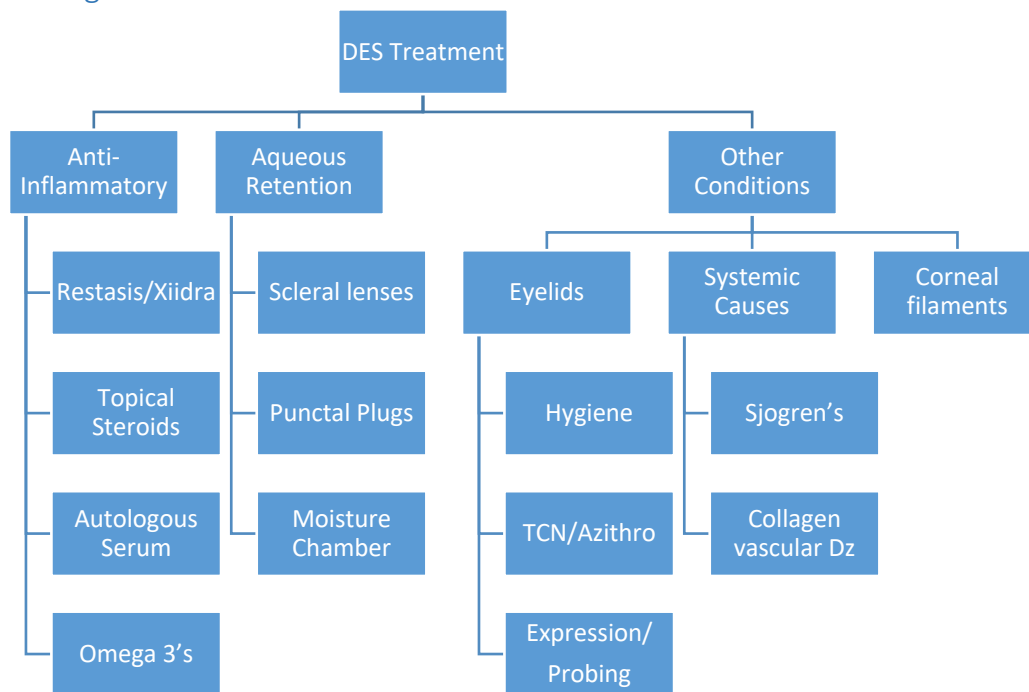
Diagnosis

There have been many studies that have looked at the reliability of different testing in patients with dry eye, these tests focus on both signs and symptoms. While there are many special tests that are only available in a limited number of locations, this document will focus on readily available tests to aid in the diagnosis of dry eye and also to classify the underlying etiology of the problem [1].

1. Standardized, validated questionnaires
 - a. Standard Patient Evaluation of Eye Dryness (SPEED)
 - b. Ocular Surface Disease Index (OSDI)
 - c. Dry Eye Questionnaire (DEQ)
 - d. McMonnies
2. Ocular surface staining
3. Eyelid evaluation
 - a. Meibography
 - b. Expression
4. Tear film break up time
 - a. Non-invasive tear film break up time
5. Tear Osmolarity
 - a. Showed that a cutoff of Osmolarity > 308 mOsm/L showed a sensitivity of 81% and a specificity of 80% [9]
 - b. Showed that a cutoff of Osmolarity > 312 mOsm/L showed a sensitivity of 73% and a specificity of 92% [10]
6. Inflammation testing

- a. Inflammadry showed sensitivity of 85% (in 121 of 143 patients), specificity of 94% (59 of 63), negative predictive value of 73% (59 of 81), and positive predictive value of 97% (121 of 125) [11].
7. Sjogren antibody testing (when indicated)

Treatment Algorithm



Literature Update

Are topical steroids safe and effective at treating signs and symptoms of dry eye [12]?

- A retrospective study compared the treatment effect of topical loteprednol etabonate 0.5% (group A, n=66) or fluorometholone 0.1% (group B, n=67) twice daily and monitored results over 2 years in patients with severe SSDE.
 - VA and IOP were not changed significantly during follow-up in either group. **Schirmer test results, keratoepitheliopathy, and symptom scores at 6, 12, 18, and 24 months (p<0.05) and tear film BUT at 12, 18, and 24 months (p<0.05) significantly improved after treatment compared with baseline in both groups.**
 - No significant differences between the groups were found in any parameter during follow-up. At 24 months, the number of patients with IOP elevation of more than 2 mmHg compared with baseline was 4 in group A (6.1%) and 9 in group B (13.4%).

Can topical steroids improve tear osmolarity [13]?

- A clinical trial evaluating the use of pulsed topical 1% methylprednisolone OU QID found that an 8 week pulsed dose can control symptoms and reduce tear osmolarity (lower the number) and reduce cytokines.

Is anti-inflammatory doxycycline effective at treating rosacea [14]?

- Multiple phase 3 clinical trials evaluating the effectivity of 40 mg QD dosing of doxycycline . This low dose yields anti-inflammatory effect without anti-microbial effects. This can reduce the risk of candida infection as well as drug resistance.
 - The mean lesion count at baseline was approximately 20 in each study arm. At week 16, the mean change from baseline in lesion count in the active-treatment groups was -11.8 in study 301 and -9.5 in study 302 compared with -5.9 and -4.3, respectively, in the placebo groups ($P < .001$ for both comparisons).
 - **This effect occurred as early as 3 weeks after initiating medication.**
 - Anti-inflammatory dose doxycycline was well tolerated; the most common adverse events were nasopharyngitis (4.8%), diarrhea (4.4%), and headache (4.4%).

How long should we keep an amniotic membrane in place [15]?

In a retrospective review of 10 patients with moderate-to-severe dry eye that was refractory to conventional maximal medical treatments were treated with self-retained cryopreserved amniotic membrane (PROKERA® Slim [PKS], Bio-Tissue, Miami, FL). Patients' symptoms, use of medications, conjunctival inflammation, corneal staining, and visual acuity were compared before and after treatment.

RESULTS:

- PKS was placed in 15 eyes of the 10 patients for 4.9 ± 1.5 days. All patients experienced symptomatic relief for a **period of 4.2 ± 4.7 months** ($P < .001$).
- Such improvement was accompanied by reduction of OSDI scores ($P < .001$), use of topical medications ($P < .001$), conjunctival hyperemia ($P < .001$), corneal staining ($P < .001$), and improvement of the visual acuity ($P = .06$).
- Linear regression analysis estimated that the **optimal duration of PKS placement was 5 days** to achieve an average symptom-free duration of 4 months in patients with dry eye.
- Interestingly, PKS placement also generated improvement in the contralateral eyes.

What ocular conditions are associated with sleep apnea [16]?

A recent literature review on obstructive sleep apnea (OSA) found that there is an increasing prevalence of OSA due to rising obesity. While OSA primarily impacts the upper airway during sleep, its physiological impact on other parts of the body is now well recognized. This review specifically evaluated the ocular conditions found at higher rates in patients with sleep apnea. These conditions include:

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|---|------------------------------------|
| • Glaucoma | • Keratoconus |
| • Floppy eyelid syndrome | • Age-related macular degeneration |
| • Nonarteritic ischaemic optic neuropathy | • Diabetic retinopathy |

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