Guideline Summary

Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Report Executive Summary

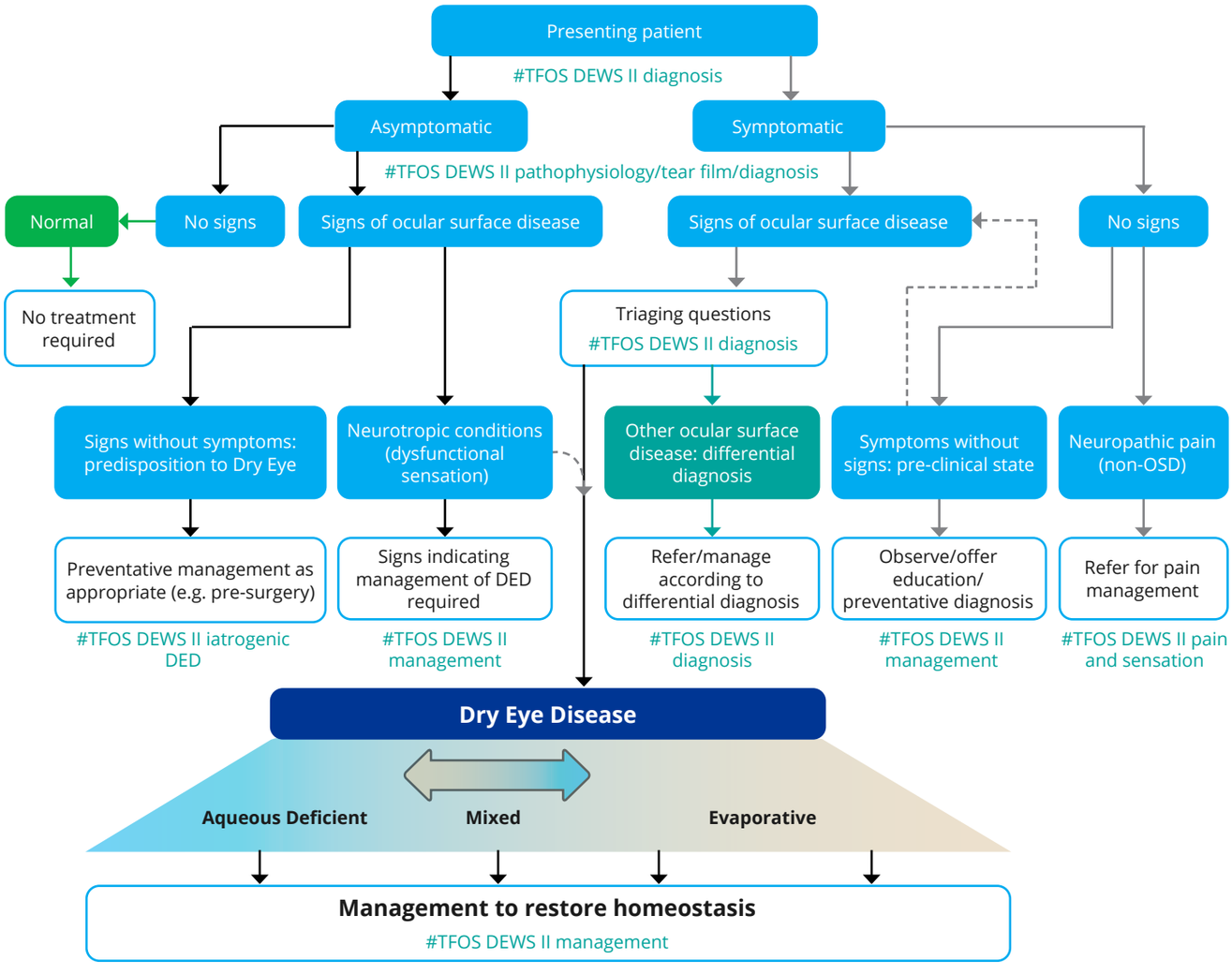
Introduction to Dry Eye Disease (DED) and its Classification

"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."[1]

Classification of DED

DED is classified based on its pathophysiology in which Aqueous Deficient Dry Eye (ADDE) and Evaporative Dry Eye (EDE) exist as a continuum so that each element can be considered for the diagnosis and management of DED.[1]

Figure 1: Classification of DED[1]



- The upper portion of the figure represents a clinical decision algorithm, which begins with symptom evaluation, followed by an investigation for the signs of ocular surface disease.[1]
- The lower portion represents the etiological classification of DED, which focuses on the 2 main categories – ADDE and EDE, and the provision of the non-mutually exclusive scenario of Mixed Dry Eye.[1]

Epidemiology

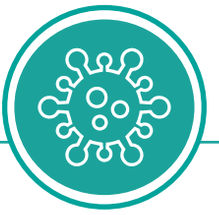
- Prevalence of DED with and without symptoms – 5% to 50%.[1]
- Higher rates of DED are reported in women than men. However, the differences become significant only with increasing age.[1]

Risk Factors

The risk factors of DED were categorized into:[1]

Consistent Risk Factors

- Age
- Sex
- Race
- Meibomian gland dysfunction
- Connective tissue disease
- Sjogren's syndrome
- Androgen deficiency
- Computer use
- Contact lens wear
- Estrogen replacement therapy
- Hematopoietic stem cell transplantation
- Environmental conditions such as pollution, low humidity, and sick building syndrome
- Medications such as antihistamines, antidepressants, anxiolytics, and isotretinoin



Probable Risk Factors

- Diabetes
- Rosacea
- Viral infection
- Thyroid disease
- Psychiatric conditions
- Pterygium
- Low fatty acid intake
- Refractive surgery
- Allergic conjunctivitis
- Medications such as anticholinergics, diuretics, and β-blockers

Inconclusive Risk Factors

- Hispanic ethnicity
- Menopause
- Acne
- Sarcoidosis
- Smoking
- Alcohol
- Pregnancy
- Demodex infestation
- Botulinum toxin injection
- Multivitamins
- Oral contraceptives

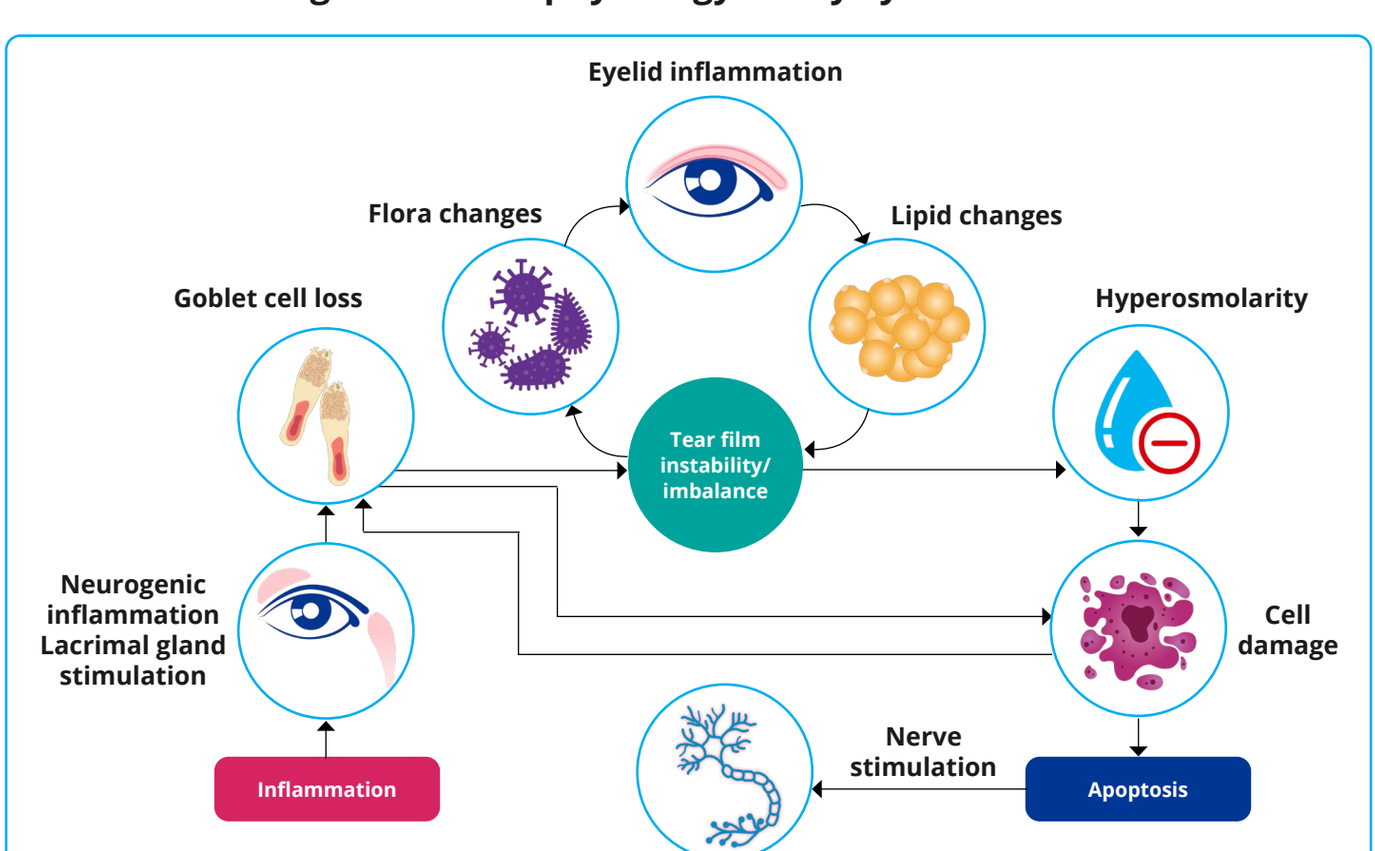
Sex, Gender, and Hormones

- The TFOS DEWS II sex, gender, and hormones report provides insights on the numerous sex-related differences in the eye that may be ascribed to the effects of sex steroids (androgens and estrogens), hypothalamic-pituitary hormones, glucocorticoids, insulin, insulin-like growth factor 1, and thyroid hormones.[1]
- Furthermore, the sex-related differences may be associated with the sex chromosome complement, which comprises the differences in parent-of-origin effects, X chromosome gene dosage (e.g., X-inactivation), genes in the non-recombining region of the Y chromosome, and from sex-specific autosomal factors and epigenetics (microRNAs, DNA methylation and acetylation, histone modifications).[1]
- Gender and biological sex play a major role in DED risk, presentation of the disease, immune responses, pain, care-seeking behaviors, service utilization, and various other parameters of eye health.[1]

Pathophysiology and Mechanism

- The core mechanism of DED is evaporation-induced tear hyperosmolarity, which is a distinctive feature of the disease. The ocular surface is damaged directly and through the initiation of inflammation.[1]
- The 2 primary forms of DED include ADDE and EDE. In ADDE, tear hyperosmolarity occurs due to a reduction in the lacrimal secretion in conditions of normal evaporation from the eye. In contrast, the tear hyperosmolarity in EDE is caused by excessive evaporation from the exposed tear film in the presence of a normally functioning lacrimal gland.[1]

Figure 2: Pathophysiology of Dry Eye Disease[2-4]



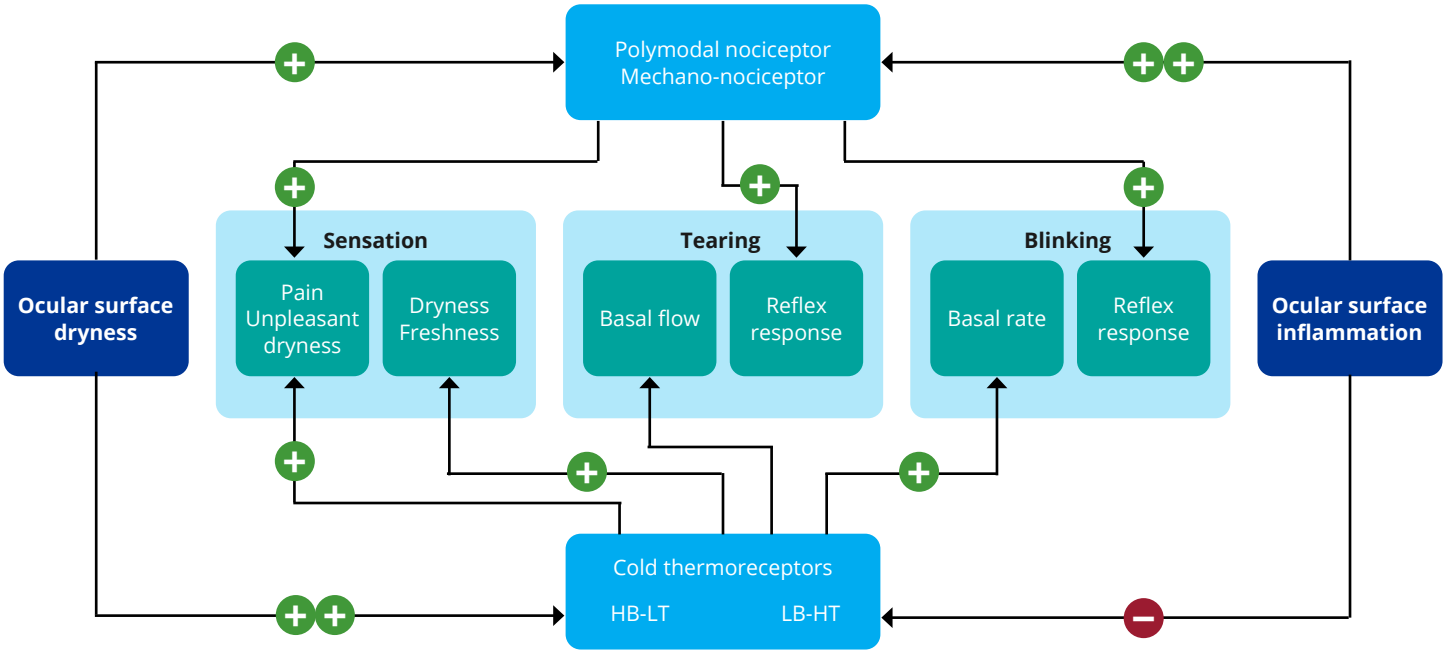
Tear Film

- The tear film consists of a lipid layer overlying a muco-aqueous phase. It is plausible that the interactions of the entire tear film, which comprises lipids, mucins, proteins, and salts, prevent evaporation and collapse.[1]
- The muco-aqueous layer contains 4 major mucins and over 1500 types of proteins and peptides. Although tear proteins reportedly vary in tears from DED patients, there is no validation yet of any set of proteins, which can help in making the diagnosis.[1]
- There is a necessity for a holistic approach to understanding the structure and function of the tear film to provide better treatment for the patients with DED.[1]

Pain and Sensation

- Pain can be categorized as nociceptive and neuropathic.[1]
- Nociceptive pain occurs in response to actual/threatened damage to the tissues, while neuropathic pain is caused by a lesion within the somatosensory nervous system.[1]
- The pain caused by DED is transmitted through the peripheral axons of trigeminal ganglion (TG) neurons, which innervates the cornea and conjunctiva. The sensory nerves belong to polymodal nociceptor neurons, pure mechano-nociceptor neurons, and cold thermoreceptor neurons.[1]
- Polymodal nociceptors respond to chemical, mechanical, and thermal stimuli and are sensitized by the inflammatory mediators released during injury. Transient receptor potential cation channel subfamily V member 1 (TRPV1) plays a vital role in sensory transduction and sensitization of the polymodal nociceptors.[1]
- Pure mechano-nociceptors respond only to mechanical forces via piezo2 and other nonidentified transducing channels, while the cold thermoreceptors continuously discharge nerve impulses at the normal temperature of the eye surface by either increasing or decreasing the basal firing frequency with cooling or warming, respectively. The main cold-transducing channel is TRPM8, which is sensitive to increased osmolarity.[1]
- The ocular surface TG neurons project primarily into 2 spatially discrete regions within the trigeminal brain stem nuclear complex: the transition region between caudal Vi and Vc (ViVc transition) and at the Vc/upper cervical cord junction (VcC1 region). Research has suggested that the VcC1 region plays a pivotal role in sensory-discriminative aspects of ocular pain.[1]

Figure 3: Ocular Inflammation of Various Etiologies or Ocular Surface Drying in DED Provokes Variable Increases (+) or Decreases (−) of Nerve Impulse Activity in Polymodal- and Mechano-nociceptors and in Cold Thermoreceptors of the High Background, Low Threshold (HB-LT) and Low Background, High Threshold (LB-HT) Types[1]



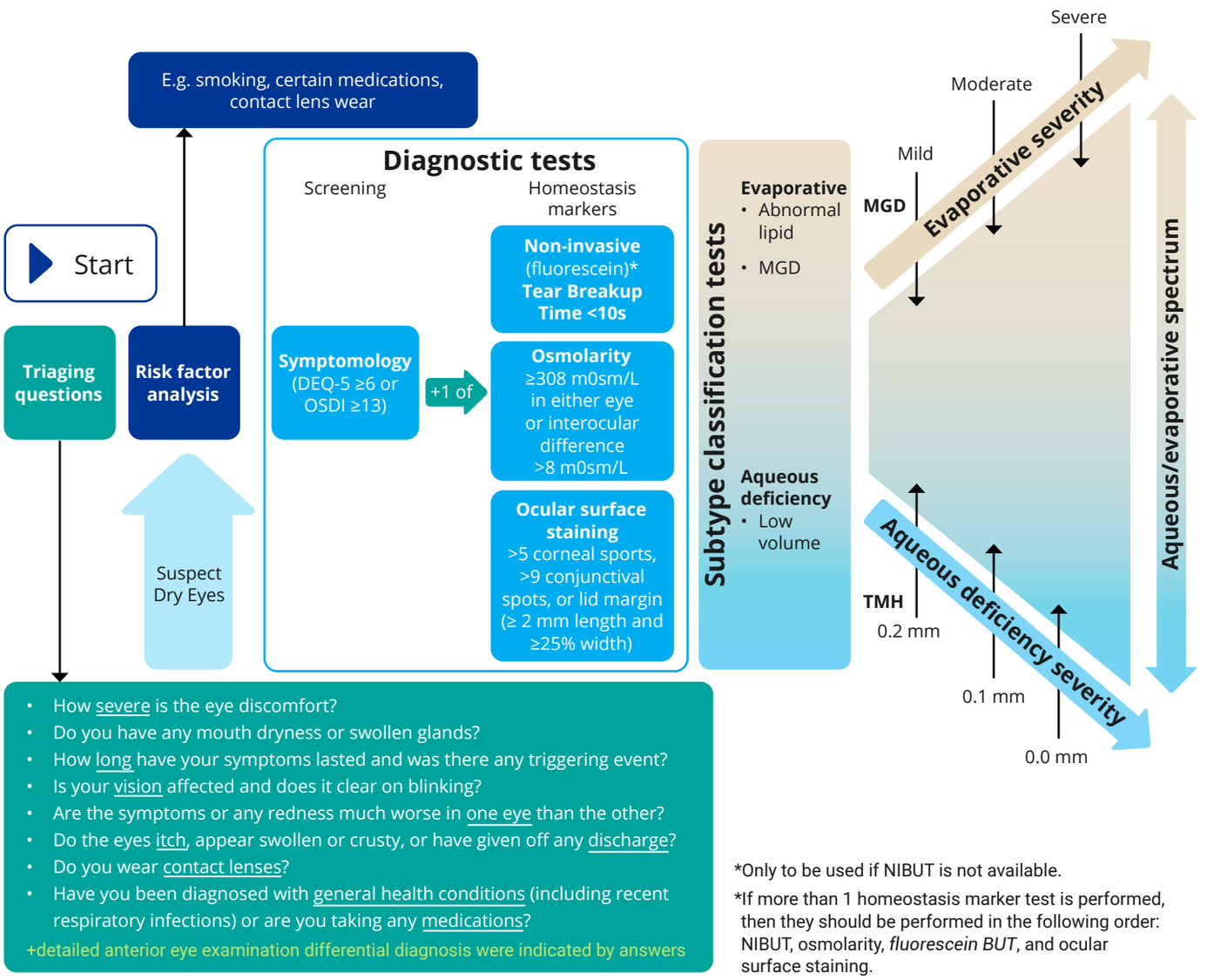
Iatrogenic Dry Eye

- DED can occur due to various iatrogenic interventions, such as topical and systemic drugs, contact lenses, and ophthalmic surgical and non-surgical procedures.[1]
- Topical medications that cause DED interact with the ocular surface by causing allergic, toxic, and immuno-inflammatory effects, whereas the preservatives can lead to the exacerbation of DED through their toxic and proinflammatory effects, along with detergent tensioactive properties.[1]
- Additionally, systemic drugs can also cause DED secondary to decreased tear production, altered nerve input and reflex secretion, inflammatory effects on secretory glands, or direct irritation through secretion into the tears.[1]
- The tear film in patients with DED who wear contact lenses undergoes biophysical changes such as a thinner, patchy lipid layer, tear film instability, lower basal tear turnover rate, and decreased tear meniscus volume.[1]
- Surgical interventions may also aggravate DED, the reasons being the type of procedure and the use of postoperative topical drugs. Other risk factors for iatrogenic DED include cataract surgery, lid surgeries, botulinum toxin application, and cosmetic procedures.[1]

Diagnostic Approach

Before diagnosing DED, it is crucial to rule out the conditions mimicking DED with the help of a questionnaire, post which the recommended tests for the diagnosis of DED can be carried out.[1]

Figure 4: The Recommended Diagnostic Approach for DED[1]



*Only to be used if NIBUT is not available.

*If more than 1 homeostasis marker test is performed, then they should be performed in the following order: NIBUT, osmolarity, *fluorescein BUT*, and ocular surface staining.

- After the diagnosis of DED is confirmed based on the positive symptom score and 1 or more positive homeostatic marker results, additional tests, namely meibography, lipid interferometry, and tear volume measurement, should be conducted to classify and evaluate the severity of DED.[1]

Management and Therapy

- The objective of DED management is to reinstate the homeostasis of the ocular surface and tear film by breaking the vicious cycle of the disease.[1]
- The management of DED involves ongoing management rather than short-term management to address chronic sequelae.[1]

Table: Stepwise Approach for the Management and Treatment of DED[1,a,b,c]

Step 1:

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:

If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
  - Punctal occlusion
  - Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage DED[d]
  - Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
  - Topical corticosteroid (limited-duration)
  - Topical secretagogues
  - Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
  - Topical LFA-1 antagonist drugs (such as lifitegrast)
  - Oral macrolide or tetracycline antibiotics

Step 3:

If above options are inadequate consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
  - Soft bandage lenses
  - Rigid scleral lenses

Step 4:

If above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g. tarsorrhaphy, salivary gland transplantation)

[a]Potential variations within the disease spectrum are acknowledged to exist between patients, and the management options listed above are not intended to be exclusive. The severity and etiology of the DED state will dictate the range and number of management options selected from 1 or more steps.

[b]One or more options concurrently within each category can be considered within that step of the DED state. Options within a category are not ranked according to the importance and may be equally valid.

[c]It should be noted that the evidence available to support the various management options differs and will inevitably be lower for newer management options. Thus, each treatment option should be considered in accordance with the level of evidence available at the time management is instigated.

[d]The use of prescription drugs needs to be considered in the context of the individual patient presentation and the relative level of evidence supporting their use for that specific indication, as this group of agents differs widely in the mechanism of action.

Clinical Trial Design

The following measures have been recommended to improve the quality of clinical trials, optimize the resources, and increase the opportunity for novel treatment strategies for patients with DED.[1]

- Clinical trials should follow Good Clinical Practice (GCP) guidelines.[1]
- Study design, treatments, and sample size should be compatible with the investigational treatment, study objectives, and the phase of development.[1]
- The dose of a drug or biologic should not only be less than the toxic/non-tolerated level in non-clinical or previous clinical studies but should also be sufficient, in dose and frequency, to deliver therapeutic concentrations at the targeted site of action.[1]
- Duration of the treatment should be consistent with the mechanism of action and time course of effect.[1]

Summary

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.

DED is classified as ADDE and EDE.

The prevalence of DED, with and without symptoms, varies from 5% to 50% and is more common in females.

The risk factors of DED are categorized as consistent, probable, and inconclusive.

The mechanism of DED is evaporation-induced tear hyperosmolarity.

The primary goal of treatment in the management of DED is to improve the homeostasis of the ocular surface and the tear film by breaking the vicious cycle of the disease.

Abbreviations:
MGD, meibomian gland dysfunction; DED, Dry Eye Disease

References:

1. Craig JP, Nelson JD, Azar DT, *et al*. TFOS DEWS II Report Executive Summary. *Ocul Surf*. 2017;15(4):802-812.
2. Baudouin C. A new approach for better comprehension of diseases of the ocular surface. *J Fr Ophtalmol*. 2007;30:239-246.
3. Baudouin C, Messmer EM, Aragona P, *et al*. Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. *Br J Ophthalmol*. 2016;100:300-306.
4. Baudouin C, Aragona P, Van Setten G, *et al*; ODISSEY European Consensus Group. Diagnosing the severity of dry eye: a clear and practical algorithm. *Br J Ophthalmol*. 2014;98:1168-1176.