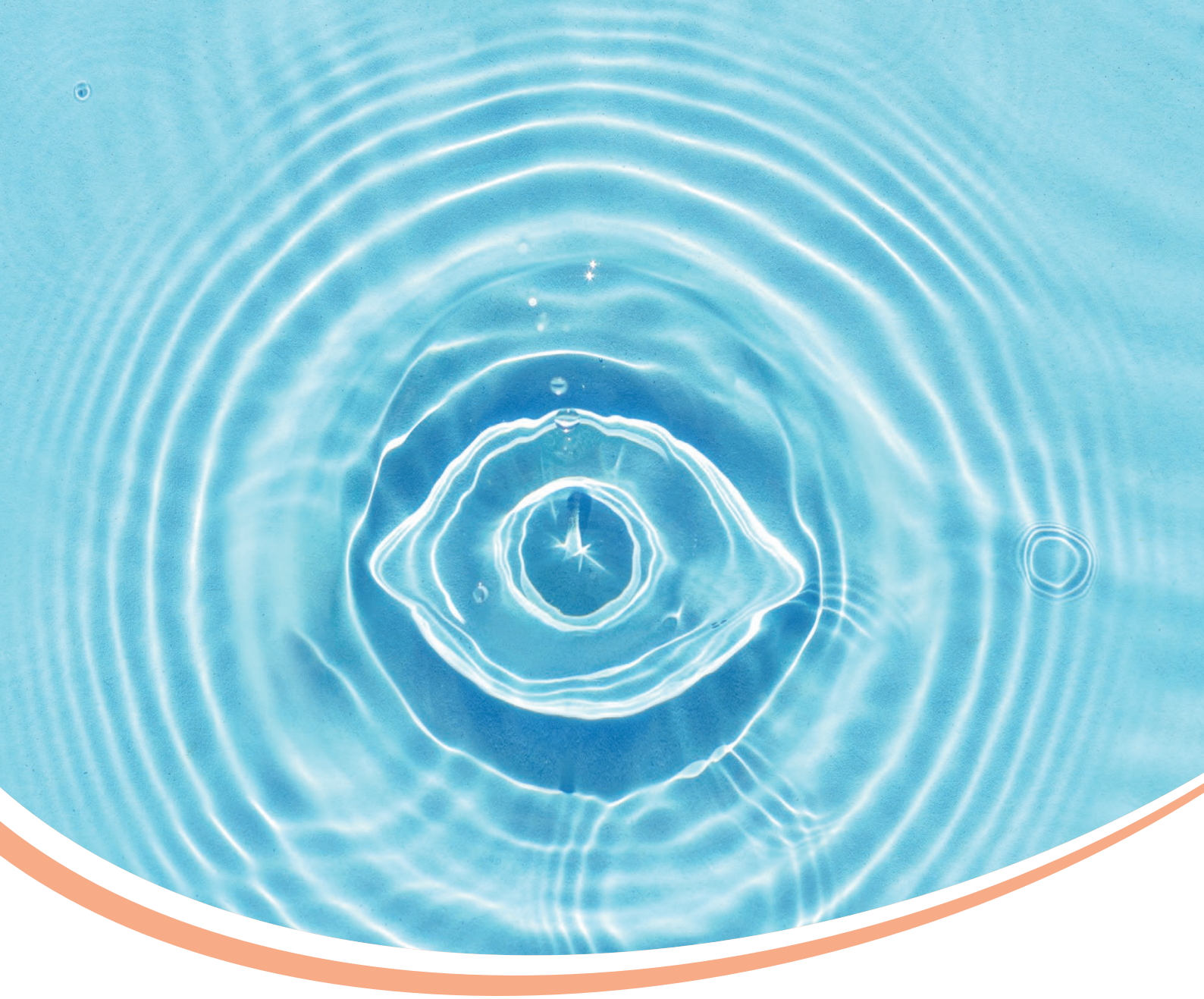


Inflammation in Dry Eye Disease

Inflammation as a central player in Dry Eye Disease: Mechanisms and steroid-based therapeutics

Théa
let's open our eyes

Contents

List of abbreviations

ADDE	Aqueous-Deficient Dry Eye
AIDS	Acquired immune deficiency syndrome
APC	Antigen-presenting cell
ATS	Artificial tear substitute
BAK	Benzalkonium chloride
CFS	Corneal fluorescein staining
CsA	Cyclosporine A
DED	Dry Eye Disease
DTS	Dysfunctional tear syndrome
DEWS	Dry Eye Workshop
EDE	Evaporative Dry Eye
GR	Glucocorticoid receptor
HADS	Hospital anxiety and depression scale
HIV	Human immunodeficiency virus
HTLV1	Human T-cell lymphotropic virus
HC	Hydrocortisone
IOP	Intraocular pressure
KCS	Keratoconjunctivitis Sicca
MAP	Mitogen-activated protein
MGD	Meibomian Gland Dysfunction
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
NSAID	Non-steroidal anti-inflammatory drug
OSDI	Ocular Surface Disease Index
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of life
TFBUT	Tear Film Break-Up Time
SHS	Subjective happiness scale
SS	Sjögren's syndrome
TLR	Toll-like receptor
VTU	Video terminal use

List of figures

List of tables

Section 1:

Introduction

Dry Eye Disease (DED) is a major and increasing healthcare problem due to its prevalence and its impact on patients' quality of life and healthcare resources. It is clear that this rather underappreciated condition should be regarded as a serious public health problem that is worthy of diagnosis and effective treatment.

Dry Eye Disease cannot be reduced merely to a simple deficiency in tear production. It covers a complex pathology in which the balance of the tear film/corneoconjunctival surface couple is disrupted. DED is caused by conditions that increase evaporation of the tear film or decrease tear production. The resulting increase in hyperosmolarity of the tear film leads to ocular surface inflammation, ocular damage and symptoms such as dryness, burning or stinging, grittiness, foreign body sensation, blurred or fluctuating vision, watery eyes, and photophobia.[1]

Understanding of the pathology of Dry Eye has significantly improved over the last decade, and recent investigations confirmed that a chronic immune inflammatory response plays a key role in the pathogenesis of human DED. Regardless of the Dry Eye aetiology, each cause of Dry Eye may act through a common pathway which primarily involves hyperosmolarity of the tear film and ocular inflammation. Inflammation probably leads to a vicious cycle that reinforces itself with each repetition of ocular stress, leading to chronicity and increasing disease severity.[1,2]

Regarding treatment options, artificial tear substitutes (ATS) have been used to treat DED for decades and are currently considered as the mainstay in the treatment of this ocular surface disorder. There is, however, a need for new treatment options targeting the cause of the disease, or at least to break the inflammatory vicious cycle at different stages of the disease.

Anti-inflammatory therapies can modulate the degree of inflammation in DED and ameliorate the damaging effects of the inflammation on the ocular surface.[2] Some topical anti-inflammatory treatments (e.g. topical corticosteroids or Cyclosporine) are already available and are indicated in severe or moderately severe DED. More recently, soft corticosteroids have been proposed to treat inflammation of the ocular surface.

Section 2:

What is Dry Eye Disease?

2.1 Definition and classification

In 2007, the International Dry Eye Workshop (DEWS) established the state-of-the-art of Dry Eye Disease, and gave a comprehensive review of its pathogenesis, natural history, and methods used to diagnose the condition.[1]

This definition of DED proposed by the DEWS has been endorsed worldwide. DED is not simply a disease of lacrimal glands deficiency, but also:

- A multifactorial disease
- A disease of the tears and ocular surface
- Results in symptoms, discomfort, and visual disturbance
- Results in tear film instability with potential damage to the ocular surface
- Is accompanied by increased osmolarity of the tear film
- Is accompanied by inflammation of the ocular surface

This definition was revised in 2017 with the publication of the second DEWS report (DEWS II). The new definition recognises the multifactorial nature of Dry Eye as an ocular surface disease where loss of homeostasis of the tear film is the central pathophysiological concept. Ocular symptoms, as a broader term that encompasses reports of discomfort or visual disturbance, feature in the definition; and the key aetiologies of tear film instability, hyperosmolarity, ocular surface inflammation and damage were all deemed important enough for inclusion in the definition.[3]

A multifactorial disease

DED is classified into two major categories, i.e. Aqueous-Deficient Dry Eye (ADDE), in which a reduction in the amount of tears produced is the primary aetiology; and Evaporative Dry Eye (EDE), in which aqueous tear production is adequate, but increased tear evaporation induces tear film instability (Figure 1).

Aqueous-Deficient Dry Eye disease (ADDE) may be subdivided into Sjögren (SS) or non-Sjögren, the former being an autoimmune disease of the lacrimal and salivary glands; and the latter being due to various disorders of the lacrimal functional unit, such as lacrimal gland insufficiency or ductal obstruction.

Meibomian Gland Dysfunction (MGD) is the leading cause of EDE, and is also frequently found in ADDE.[4] MGD is a chronic, diffuse abnormality of the meibomian glands, commonly characterised by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion.[4] The proportion of subjects exhibiting signs of Evaporative Dry Eye resulting from MGD far outweighs that of subjects with pure ADDE. In a general clinic-based cohort of patients with DED, 224 subjects classified with DED using an objective, composite, disease severity scale, 159 (71%) were classified into one of the three following categories: 79 (31%) were classified with only MGD; whereas only 23 (9%) were classified as purely aqueous deficient; and 57 (25.4%) showed evidence of both MGD and ADDE. Overall, 86% of these qualified DED patients demonstrated signs of MGD. The remaining 65 (29%) patients showed evidence of DED through other clinical signs, without overt evidence of MGD or ADDE, possibly because of the inherent variability of these signs.[5]

Figure 1. Aetiologic cause of Dry Eye.[6]

Aqueous-Deficient Dry Eye (ADDE)

Sjögren Syndrome Dry Eye (SSDE)

Associated systemic diseases

- Rheumatoid arthritis
- Polyarteritis nodosa
- Systemic lupus erythematosus
- Wegener granulomatosis
- Systemic sclerosis
- Primary biliary cirrhosis
- Mixed connective tissue disease

Non-Sjögren Syndrome Dry Eye (NSDE)

Intrinsic Lacrimal Gland Deficiency

- Lacrimal gland ablation
  - Congenital alacrima
  - Triple A syndrome

Age-related ADDE

Inflammatory and Other Lacrimal Gland Infiltration

- Sarcoidosis
- Lymphoma
- Viral Infection
- Radiation Injury

Lacrimal Gland Obstruction

- Cicatricial conjunctivitis
  - GVHD
  - Stevens-Johnson Syndrome/TEN
  - Mucous Membrane Pemphigoid
  - Cicatricial Pemphigoid
  - Pemphigus
  - Trachoma
  - Chemical Injury

Hyposecretory States – Failure of the Lacrimal Functional Unit

- Reflex Afferent Block
  - Topical anaesthesia
  - Trigeminal Nerve Injury
    - Refractive Surgery
    - Neurotrophic Keratitis
- Secretomotor Block
  - Parasympathetic damage
  - Pharmacological Inhibition
- Combined Afferent and Efferent Block
  - Familial Dysautonomia

Other Disorders

- Meige Syndrome
- Diabetes Mellitus
- Pseudoexfoliation

Evaporative Dry Eye (EDE)

Meibomian Gland Diseases

Lid-Related

Meibomian Gland Dysfunction (MGD)

- Primary
  - Meibomian Seborrhea
  - Obstructive MGD
  - Cicatricial/Non-Cicatricial
- Secondary to local disease
  - Anterior Blepharitis
  - Ocular surface inflammation
  - Contact Lens Wear
- Secondary to systemic dermatoses
  - Rosacea
  - Seborrheic dermatitis
  - Atopic dermatitis
  - Ichthyosis
  - Psoriasis
- Secondary to Chemical Exposure
  - 13-cis retinoic acid
  - Polychlorinated biphenols
  - Antiandrogens

Genetically Determined Meibomian Gland Diseases

- Meibomian Agenesis and Distichiasis
- Anhidrotic ectodermal dysplasia
- Ectrodactyly syndrome
- Epidermolysis Bullosa
- Ichthyosis follicularis
- Turner syndrome

Disorders of Lid Aperture, Congruity, Dynamics

- Blink-related
- Parkinson's Disease

Ocular Surface-Related Evaporative Dry Eye

- Allergic Eye Disease
- Vitamin A Deficiency
- Short Break-Up Time Dry Eye
- Iatrogenic Disease

Additionally, DED can be categorised as episodic or chronic. Episodic Dry Eye occurs when environmental or visual tasks with reduced blinking overwhelm the stability of the tear and produce symptomatic Dry Eye. This notable chronic Dry Eye, although aggravated by the same environmental conditions, persists continuously with symptoms and possible damage to the ocular surface.[7]

DED is a disease of the tears and ocular surface

DED is a progressive and chronic condition of the lacrimal and meibomian glands that leads to reduced aqueous tear production and increased tear evaporation.[8] Factors that disturb the delicate homeostatic balance of the ocular surface system (Table 1) can adversely affect tear film instability and osmolarity, resulting in osmotic, mechanical and inflammatory damage.[9]

Table 1. The ocular surface system

Cornea
Conjunctiva
Lacrimal glands
Meibomian glands
Lacrimal drainage system
Connected neural network

The tear film exerts an essential nutritional and protective role for good health of the ocular surface. Its quantitative or qualitative alteration is predominant in Dry Eye. Because the tear film in Dry Eye patients is unstable and incapable of maintaining the protective qualities that are necessary for its structure and function, patients experience the discomfort symptoms associated with Dry Eye, which are burning, stinging, grittiness, foreign body sensation, tearing, ocular fatigue, and dryness. Patients may complain of symptoms of Dry Eye in the presence, or absence, of signs of the disease. Additionally, Dry Eye may also be diagnosed based only on the signs observed by a healthcare professional in the absence of symptoms/complaints by the patients.[7]

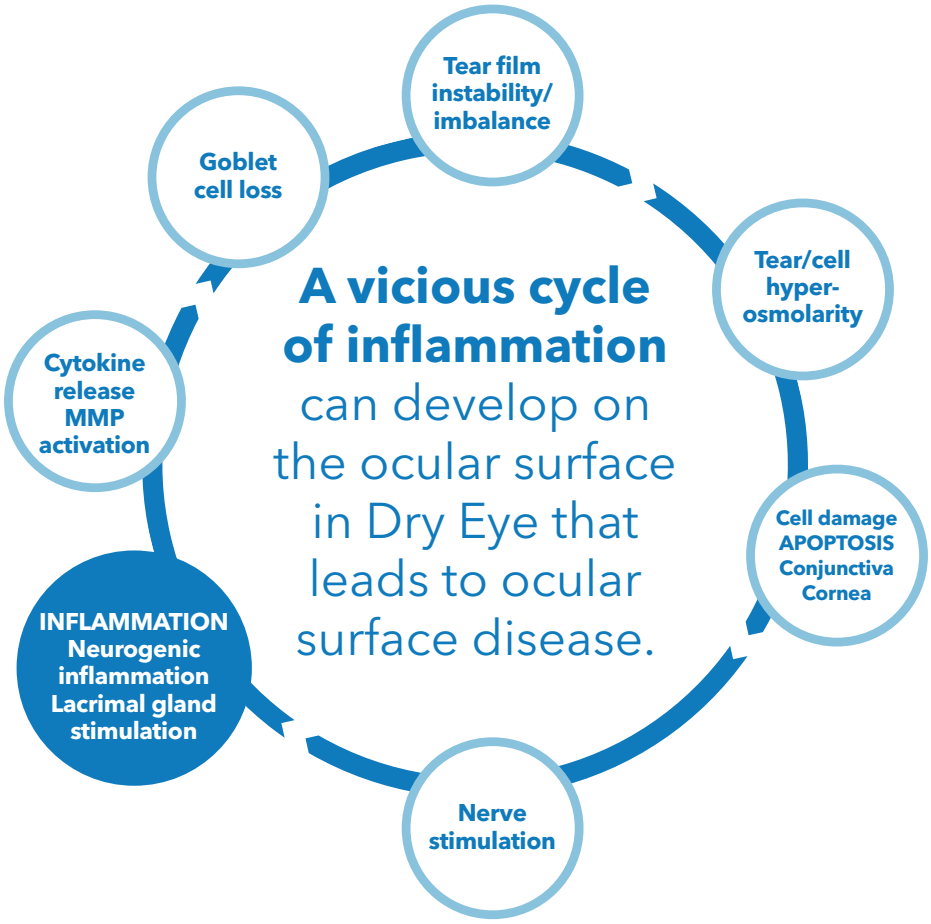
Hyperosmolarity of the tear film

DED is caused by conditions that increase evaporation of the tear film or decrease tear production. Elevated tear osmolarity has been reported to be a global marker (present in both subtypes of the disease: Aqueous-Deficient Dry Eye and Evaporative Dry Eye). The resulting increase in tear film osmolarity leads to ocular surface inflammation, damage, and symptoms.[1,2]

Inflammation of the ocular surface

Hyperosmolar stress is, by itself, proinflammatory, and inflammation is considered as a central feature of ocular surface disease. It is clear that patients do not necessarily have a systemic autoimmune disease to experience a local autoimmune event.[10]
Regardless of the aetiology or subtype of DED, tear film hyperosmolarity induces ocular surface damage and inflammation, which represents a common pathway of DED pathogenesis.
No matter how the cycle starts, once it's established it can lead to a severe treatment-refractory ocular surface disease and permanent damage if no corrective treatment is given.[11] (Figure 2).

Figure 2. The vicious cycle of inflammation in DED



Adapted from Baudouin C, et al. Br J Ophthalmol. 2016.[11]

2.2 Disease severity

DED is responsible for many subjective symptoms, which are largely non-specific. Patients suffering from DED often feel pain, itching, foreign body sensation, burn sensation, photophobia and general discomfort.[1,12] Symptoms may, however, cover various degrees of severity, from discomfort to painful chronic conditions. DED can lead to corneal and conjunctival damage such as Keratoconjunctivitis Sicca (KCS) and corneal ulceration, which can evolve to visual impairment and decreased quality of life.

Disease severity is one of the most relevant factors when considering treatment options.[13] In clinical practice, most patients generally present with both symptoms and clinical signs. However, it must be pointed out that some patients may be asymptomatic and others may present symptoms without clinical signs, as assessed by standard objective tests i.e. Tear Film Break-Up Time (TFBUT), Schirmer test, and corneal or conjunctival staining.[8,12] As reviewed recently by a European Consensus Group (ODYSSEY Consensus Group),[12] in early and mild DED, the presence of hyperalgesia can cause significant ocular discomfort, without signs of tissue damage. In more severe or chronic disease, decreased corneal sensitivity due to compensatory reflex mechanisms can actually reduce discomfort. This explains why symptomatology alone is a poor indicator of disease severity in some DED patients.

The severity scale adopted in 2007 by the DEWS considers four levels of severity, based on increasing frequency and intensity of various signs and symptoms (Table 2).[1] The ODYSSEY Consensus Group proposed a new algorithm to diagnose severe DED, based on a tear film instability (TFBUT) as a prerequisite; and the presence of severe symptomatology (as assessed by an ocular surface index (OSDI*) ≥ 33); and severe ocular damage, assessed by a corneal fluorescein scale (CFS) ≥ 3. In case of discordance between symptomatology and corneal damages, additional criteria should be considered (e.g. conjunctival staining, Schirmer test, impaired visual function (blurred vision), filamentary keratitis, tear hyperosmolarity, or impression cytology, blepharospasm, and MGD or eyelid inflammation).

Since the DEWS, tear osmolarity is considered as the hallmark of DED. Tear film osmolarity is thought to be the single best marker of disease severity across normal, mild/moderate, and severe categories; while other tests, such as Schirmer test without anaesthesia, TFBUT, corneal staining, meibomian dysfunction assessment, conjunctival staining, and Dry Eye symptom questionnaire, were found to be informative in the more severe forms of disease.[14]

However, the TFOS DEWS II in 2017 considered that tables of severity describing several signs and symptoms and (often arbitrary) cut-offs for different levels are of

limited use, as features of Dry Eye often do not show strong association. Hence it is recommended that severity, for the purpose of selecting treatment, is based on subtype classification features (MGD, lipid thickness/dynamics and non-invasive tear volume), along with symptomology.[15]

*For details on OSDI score, see *Schiffman RM, et al. 2000.*[16]

Table 2. Dry Eye severity level according to DEWS 2007.[1]

Dry Eye severity level	1	2	3	4*
Discomfort, severity & 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 injections	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, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinisation, symblepharon
TFBUT (s)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5min)	Variable	≤10	≤5	≤2

*severity level 4 must have signs and symptoms
TFBUT: Fluorescein Tear Film Break-Up Time; MGD: Meibomian gland disease

2.3 Current therapeutic options

In general, therapy is based upon the severity and chronicity of the Dry Eye Disease and the patient response to each added therapy.[17]

Dry Eye is a disease with various clinical manifestations. The first step in disease management is to identify the underlying aetiology and to try to eliminate it and/or treat it. Afterwards, and regardless of the aetiology, the mainstay first-line therapy is external augmentation of the tear film with topically administered artificial tear substitutes (ATSs).[7]

ATSs are recommended in the first-line therapy for DED. They are the treatment of choice for mild forms of Dry Eye. In cases of moderate disease, artificial tears may be used as first-line treatment but the rate of application may be increased, compared to mild forms.

In severe cases, artificial tears may be used in combination with other treatments (moist chamber goggles, inserts, occlusion of the lacrimal ducts...), and anti-inflammatory drugs.[18]

An increasing strategy is to target the ocular inflammation with available treatment options such as including corticosteroids, Cyclosporine A, or Tetracycline.[17,19]

A proposed therapeutic strategy, according to the level of Dry Eye severity, is summarised in Table 3.

Table 3. Treatment strategy according to disease severity levels*

Level 1 (mild)	Level 2 (moderate)	Level 3 (severe)	Level 4 (disabling)
Artificial tears Omega-3 fatty acids	Artificial tears Mucin secretagogues Steroids Cyclosporine A	Autologous serum Oral tetracyclines Punctal plugs	Systemic immunosuppression Moisture goggles, prosthetic lens, surgery (tarsorrhaphy, AMT)

* According to the DEWS 2007.[18]; *Adapted from Stern M.E, et al. Int Rev Immunol. 2013.*[19]

In 2017, the DEWS II published a step-by-step algorithm for the management of Dry Eye.[20] A list of a series of management and treatment options that have all been shown to result in alleviation of presenting DED was proposed. Should patients not respond to a given level of management, or should they present with more severe DED, the next level of management is recommended – and in some cases, the previous therapy may be continued in addition to any new therapies.

Step 1	Step 2	Step 3	Step 4
Education regarding the condition, its management, treatment and prognosis	Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)	Oral secretagogues	**Topical corticosteroid** for longer duration
Modification of local environment	**Topical corticosteroid** (limited-duration)	Autologous/allogeneic serum eye drops	Amniotic membrane grafts
Education regarding potential dietary modifications (including oral essential fatty acid supplementation)	Topical secretagogues	Therapeutic contact lens options - Soft bandage lenses - Rigid scleral lenses	Surgical punctal occlusion
Identification and potential modification/elimination of offending systemic and topical medications	Topical non-glucocorticoid immunomodulatory drugs (such as Cyclosporine)		Other surgical approaches (e.g. tarsorrhaphy, salivary gland transplantation)
Ocular lubricants of various types	Topical LFA-1 antagonist drugs (such as lifitegrast)		
Lid hygiene and warm compresses of various types	Oral macrolide or tetracycline antibiotics		

Section 3:

Impact on quality of life

The fact that DED impacts quality of life (QoL) is not trivial.[7] Observational studies have confirmed that DED may have a considerable impact on visual function, daily activities, social and physical functioning, workplace productivity, and on the overall QoL. According to the DEWS,[21] the impact of Dry Eye on quality of life is mediated through:

- Pain and irritation symptoms
- Effect on ocular and general health and wellbeing
- Effect on perception of visual function
- Impact on visual performance

Even in the presence of only chronic ocular irritation or discomfort, the impact on the patient's QoL may be important, due to the detrimental psychological effect caused by an almost permanent pain, despite current use of ATSs to relieve symptoms.[11] In some cases, a chronic ocular pain, even mild, can turn into real depression. This was clearly demonstrated in a population-based study in participants older than 40 years (N=229, mean age 60.7±10.1 years, 60% of females). In this study, Dry Eye was defined as the simultaneous presence of symptoms and one sign (i.e. TFBUT ≤ 10 sec; or Schirmer test ≤ 5 mm, or fluorescein staining core ≥1). Overall, the QoL assessed by the NEI VSQ25 score was significantly lower in subjects with definite criteria (i.e. presence of symptoms and at least one criteria) compared to subjects without signs and symptoms. Both the ocular pain and the mental health subscale scores were significantly lower in definite DED. In addition, the total symptom score was significantly correlated with the QoL score and ocular pain subscale score as well as the mental health subscale score.[22]

Thus, a reduction in QoL is inevitable when the symptoms of Dry Eye occur, regardless of whether they are mild, transient or persistent. Using utility scores to quantify the burden of Dry Eye compared to other chronic diseases, it was found that mild Dry Eye was comparable to psoriasis; moderate Dry Eye to moderate angina pectoris (known to be disabling); and severe DED was as heavy as class III/IV angina (Table 4).[23]

Table 4. Burden of DED compared with other chronic diseases

Health state	Medical condition of subjects	Mean utility time trade-off*
Treatment with warfarin	Atrial fibrillation	0.98
Mild psoriasis	Psoriasis	0.89
Mild Dry Eye	**Dry Eye**	**0.81**
Asymptomatic Dry Eye	**Dry Eye**	**0.78**
Moderate Dry Eye	**Dry Eye**	**0.78**
Moderate angina	Angina	0.75
Severe Dry Eye	**Dry Eye**	**0.72**
Class III/IV angina	Angina	0.71
Disabling hip fracture	Hip fracture	0.65
Monocular painful blindness	**Dry Eye**	**0.64**
Severe Dry Eye with tarsorrhaphy	**Dry Eye**	**0.62**
Moderate stroke	Atrial fibrillation	0.39
Binocular painful blindness	**Dry Eye**	**0.35**
Complete blindness cataract	**Dry Eye**	**0.33**
AIDS	HIV	0.21
Major stroke	Atrial fibrillation	0.11

AIDS: Acquired immune deficiency syndrome;
HIV: Human immunodeficiency virus
*The closer the utility score is to 1.0, the better the QoL

3.1 Impact on visual function

Visual complaints are highly prevalent among Dry Eye patients. Corneal epithelial disease in DED may reduce optical performance. Many patients with tear dysfunction complain of fluctuating vision that may improve following instillation of artificial tears. These complaints are usually described as disturbed vision or blurry, foggy vision that clears temporarily with blink. Often, patients with tear dysfunction have normal visual acuity when measured by conventional methods; however, reduced visual performance has been found with more sophisticated measures of visual function. Patients with corneal epithelial disruption were noted to have greater reduction in contrast sensitivity and low-contrast visual acuity than eyes with normal tear function. A number of studies have reported increased levels of higher order aberrations, particularly coma, in eyes with tear dysfunction. Many patients with corneal epitheliopathy in DED complain of photosensitivity that, in some cases, can be severe and disabling. These alterations in visual quality lead to a reduction in functional visual acuity.[21,24]

3.2 Impact on daily activities

Several common, daily tasks are adversely affected by Dry Eye. The analysis of a subset of participants of the Women's Health Study (WHS) and of the Physicians' Health Study (PHS) demonstrated that people with Dry Eye Disease were about three times more likely to report problems with common activities, including reading, performing professional works, computer use, television watching, daytime and nighttime driving, than were those without DES (Table 5).

Table 5. DED and increased risk of problems with daily life activities.[25]

Activity	Odd ratio*	95% CI
Reading	3.64	2.45 – 5.40
Professional work	3.49	1.72 – 7.09
Computer use	3.37	2.11 – 5.38
TV watching	2.84	1.05 – 7.74
Driving daytime	2.80	1.58 – 4.96
Driving nighttime	2.20	1.48 – 3.28

Analysis adjusted on age, sex, and comorbidity
*Estimates greater than one signify that subjects with DED were significantly more likely to report having problems with that particular activity.

Similarly, a population-based study conducted in 2010 in Singapore with 3,280 people aged ≥ 40 years showed that patients with symptomatic Dry Eye reported significantly more difficulties in performing vision-related daily activities, independent of their visual acuity. The most frequent affected activities were navigating stairs, reading road signs, reading newspapers, cooking, recognising friends, watching television and driving at night.[26]

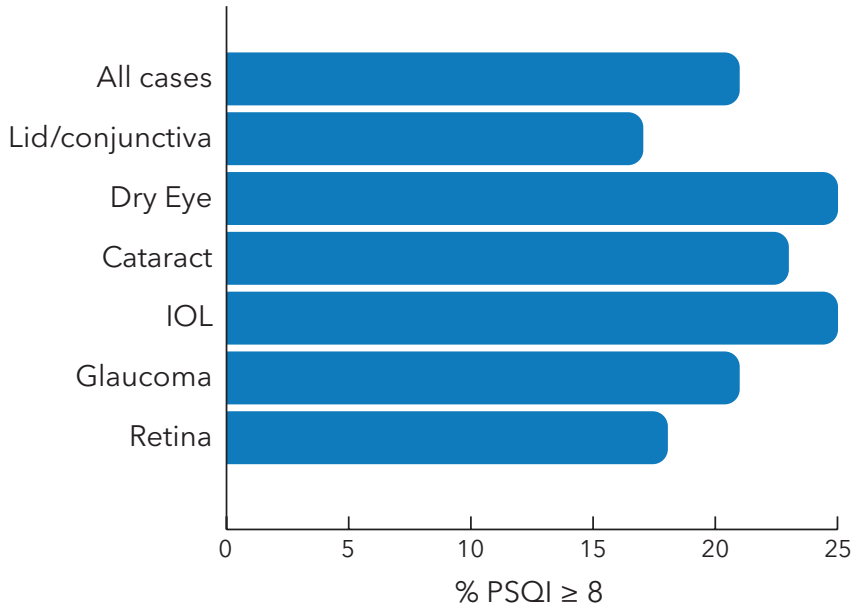
3.3 Impact on social and physical function

Results from the Beaver Dam Offspring Study show that Dry Eye Disease may be significantly associated with lower scores on health-related QoL.[27] In this study, participants who reported symptoms present, 'sometimes or more often', and, 'moderately bothersome or greater', or those who reported currently using eye drops at least once a day for Dry Eyes, were diagnosed to have DED. Dry Eye participants scored lower on the SF-36 and on the NEI-VFQ25 when controlling for age, sex, and comorbid conditions. In the SF-36, both the physical and mental component score were impaired, the largest differences being in the Bodily Pain and General Health Indices. Those with Dry Eye symptoms scored lower on all 12 of the NEI-VFQ subscales; with the largest difference appearing in the ocular pain score. In analysis controlling for age, sex, education, and a number of comorbid

conditions, those who reported Dry Eye symptoms were also 64% more likely to report depressive symptoms (score greater than or equal to 16) as measured by the CES-D. Stratification by age showed similar results.[27]

As highlighted in another recent cross-sectional study in Japan,[28] sleep and mood conditions are frequent in general eye clinic visitors. The study revealed that Dry Eye patients (mean age 61±17 years, 82% of females) had the worst scores of sleep quality, depression and anxiety compared to other eye diseases (Figures 3 & 4). This may contribute to the deteriorated QoL in these patients, and may result in considerable loss of productivity in the active working population. Thus, Dry Eye may cause a constant feeling of discomfort or distress that leads to mood disorders, especially in older patients.

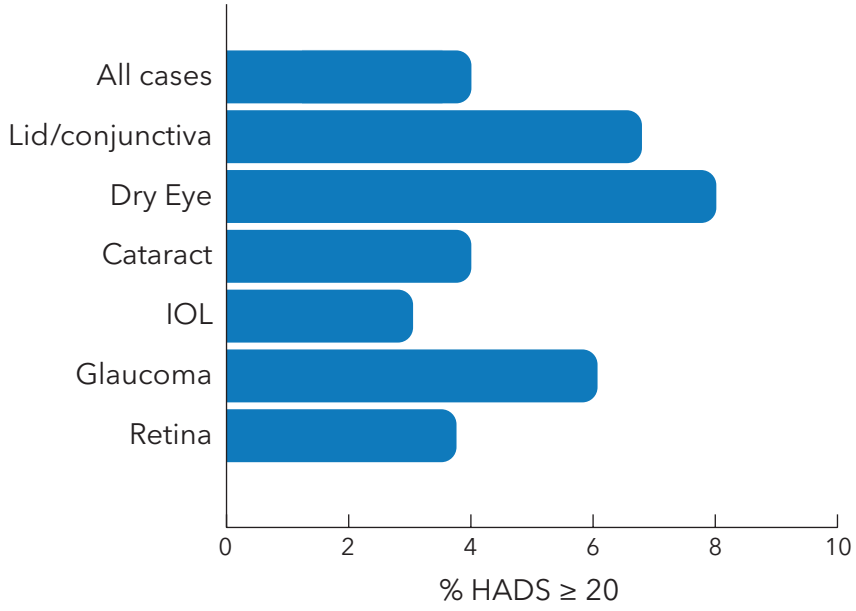
Figure 3. High prevalence of sleep disorder in patients with DED



IOL: Intraocular lens; PSQI: Pittsburgh Sleep Quality Index

Proportion of patients with sleep quality score (PSQI) ≥ 8 (indicating a clinically significant sleep disorder) among eye clinic visitors

Figure 4. High prevalence of anxiety and depression in patients with DED



HADS: Hospital anxiety and depression scale; IOL: Intraocular lens

Proportion of patients with anxiety and depression score (HADS) ≥ 20 among eye clinic visitors

Results of the OSAKA study in young and middle-aged office workers using computers (N=672) of video display terminal (VDT) also suggest that Dry Eye may impact wellbeing.[29] In this study, happiness as assessed by the Subjective Happiness Scale (SHS) was significantly and inversely correlated with the Dry Eye symptom scores ($r=-0.188$, $p<0.001$). The study also showed significantly reduced quality of sleep as assessed by the Pittsburgh Sleep Quality Index (PSQI) score in patients with Dry Eye. A total of 45% of the DED and probable-DED participants reported poor sleep quality, compared to 34% in non-DED participants. In addition, statistically significant correlation was observed between the PSQI score and the Dry Eye symptoms score ($r=-0.27$, $p<0.001$).

Section 4:

A highly prevalent disease

4.1 Prevalence

The exact prevalence of Dry Eye Disease in the general population is not known, despite several large population-based studies across the world. Estimations remain very large and were established between 5 and 30% of the population > 50 years.[21] According to the DEWS in 2007, severe to moderately severe cases probably account for the lower margin (i.e. 5%), which remains considerable. Regarding treated patients, it was reported that 15 to 25% of patients aged over 65 years regularly used artificial tear substitutes.[11]

Most population-based studies used symptom scores to assess DED. A recent observational, multicentre, retrospective analysis in the European Union and the United States, reported that more than 40% of patients diagnosed with DED are asymptomatic.[8] Thus, an important number of subjects are probably not included in these statistics. Moreover, in clinical practice, Dry Eye is probably underreported by patients who do not know they have a real ocular disease due to broadly non-specific ocular symptoms. Generally, patients do not report the problem to physicians.[7]

4.2 Risk factors

The high prevalence of DED in the general population may be explained by its multifactorial aetiology. Numerous risk factors have been hypothesised to predispose to DED, as summarised in Table 6.

Table 6. Risk factors for DED as mentioned by the DEWS II.[15]

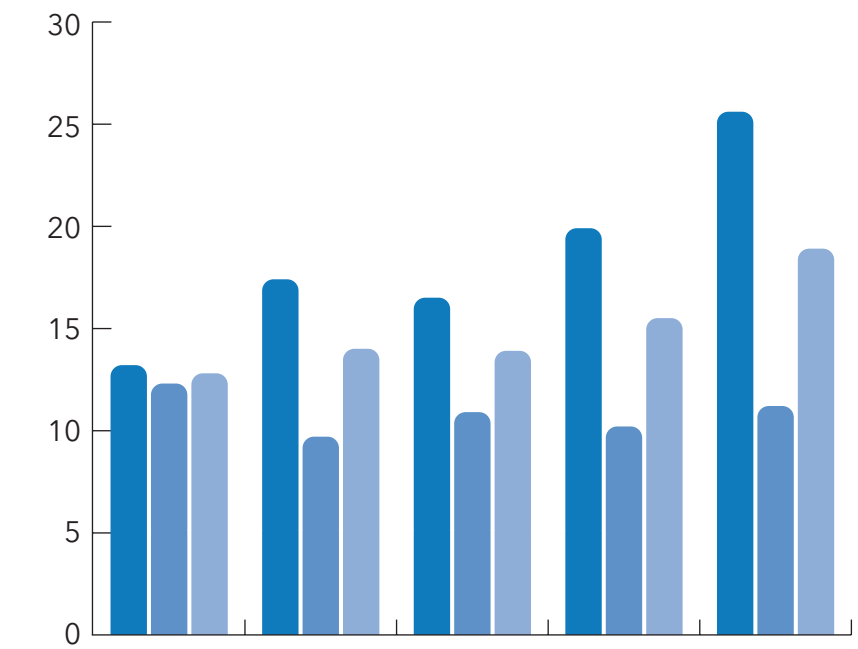
	Consistent	Probable	Inconclusive
Non-modifiable	Ageing Female gender Asian race Meibomian Gland Dysfunction Connective tissue diseases Sjögren's syndrome	Diabetes Rosacea Viral infection Thyroid disease Psychiatric conditions Pterygium	Hispanic ethnicity Menopause Acne Sarcoidosis
Modifiable	Androgen deficiency Computer use Contact lens wear Hormone replacement therapy Haematopoietic stem cell transplantation Pollution, low humidity, sick building syndrome Antihistamines, antidepressants, anxiolytics, isotretinoin	Low fatty acids intake Refractive surgery Allergic conjunctivitis Anticholinergics, diuretics, beta-blockers	Smoking Alcohol Pregnancy Demodex infestation Botulinum toxin injection Multivitamins, oral contraceptives

Age and female gender

Age and female gender are well-known major risk factors. In clinical practice, menopausal and postmenopausal women tend to have Dry Eye symptoms. In addition, sex hormone influences ocular surface conditions, probably through their effects on tear secretion, Meibomian Gland Dysfunction, and conjunctival goblet cell density.[7] Each 3-year increase in the duration of hormone-replacement therapy has been associated with a significant 15% (95% CI, 11%-19%) elevation in risk of clinically diagnosed Dry Eye syndrome or severe symptoms.[30]

The increased prevalence of Dry Eye in the elderly may be due in part to the lacrimal gland function which decreases gradually with ageing, resulting in reduced tear secretion and DED.[1,31] Results of the Beaver Dam Offspring Study showed that DED may account for 12 to 14% of the adult population aged < 45 years, compared to 19% in subjects aged over 65 years (Figure 5).[27]

Figure 5. Prevalence of DED according to age category



	21-34	35-44	45-54	55-64	65-84
Women	13.2	17.4	16.5	19.9	25.6
Men	12.3	9.7	10.9	10.2	11.2
Overall	12.8	14	13.9	15.5	18.9

Participants were asked "How often do you have dry eyes, a dry, gritty, or burning feeling?", "How much does the dryness in your eyes bother you?", "Is there a season of the year when the dryness in your eyes is the worst?", and "Are you currently using eye drops at least once a day for Dry Eye?". Participants who reported symptoms were present, 'sometimes or more often', and they were, 'moderately bothersome or greater', or those who reported currently using eye drops at least once a day for Dry Eye were considered to be cases. (Results from the Beaver Dam Offspring Study).[27]

However, the prevalence of DED among the young population should increase in the near future due to factors linked to lifestyle (e.g. central heating, air-conditioned working environments), including visual activities (e.g. reading on computer or smartphone) probably due to excessive evaporation of tear fluid attributable to prolonged blinking interval while gazing. A recent study in Japan (The OSAKA Study) showed that more than 50% of young-to-middle-age workers who used computers had probable DED (defined by the presence of 2 criteria among ocular symptoms, TFBUT < 5 sec or Schirmer test ≤ 5 mm, and epithelial damage score ≥ 3).[31] The prevalence of definite DED (defined by the presence of 3 disease criteria) in these subjects was 8% in men and 19% in women. Ophthalmic findings revealed short TFBUT and corneal staining accompanied by normal Schirmer test values. The risk of DED appears to be increased with prolonged computer use (i.e. ≥ 8 hours/day).

Lifestyle factors

DED can be influenced through various daily activities, and social and dietary habits such as smoking, which increases DED, and dietary intake of omega-3 fatty acid which reduces DED.[7] Environmental factors, such as relative humidity, indoor environment, pollution, air travel, and extreme temperatures, among others, negatively impact precorneal tear film stability and thus Dry Eye symptoms.[7]
In the Beaver Dam Offspring Study,[27] Dry Eye was independently associated with female gender, current contact lens use, allergies, arthritis, thyroid disease, antihistamine use, and steroid use. Long-term contact lens wear may precipitate or exacerbate DED as a result of cornea desensitisation over years of contact lens stimulation.[7] It is estimated that 50 to 75% of contact lens wearers experience dryness and discomfort, and this has been shown to lead to contact lens discontinuation in as many as 24% of people.[21]

Associated systemic or ocular diseases

Many systemic diseases, particularly autoimmune or immune-driven diseases, are significantly associated with the development of DED.[2] This included Sjögren's syndrome (SS), rheumatoid arthritis, scleroderma, polymyositis, lymphoma, amyloidosis, haemochromatosis, sarcoidosis, systemic lupus erythematosus, and autoimmune thyroid disease.[32] In the Physicians' Health Studies (PHS), men with treated or untreated hypertension or with benign prostatic hyperplasia were significantly more likely to have DED.[33] In a recent study in 243 patients with type 2 diabetes mellitus, 28% had DED as assessed by tear hyperosmolarity.[34]

The prevalence of DED is increased among patients suffering from other ocular diseases. For example, DED was found in 33% of patients with glaucoma or high intraocular pressure, and 41% of patients with intraocular lens.[28] Dry Eye is common in patients reporting Blepharitis, seborrheic dermatitis, acne rosacea, atopy, psoriasis which are major causes of MGD.[4]

Adverse effects of concurrent systemic therapy

Some drugs (antihistamines, antianxiety drugs, isotretinoin, antidepressants, oral steroids) have drying side effects which can promote or exacerbate Dry Eye, while angiotensin-converting enzyme inhibitors may be associated with a lower risk of Dry Eye.[35]

Preservatives in eye drops

Eye drops containing preservatives (such as benzalkonium chloride, BAK) are susceptible to promote DED directly by damaging the tear film and the ocular surface, and indirectly through proinflammatory mechanisms.[36]

Section 5:

Ocular surface inflammation and Dry Eye Disease

The understanding of the pathology of Dry Eye has significantly improved over the last decade. Regardless of the underlying aetiology, Dry Eye is associated with abnormalities in precorneal tear film with subsequent inflammatory changes in the entire ocular surface, including the adnexa, conjunctiva, and cornea.[32]

While acute inflammation may initially be accompanied by increased reflex tearing and blinking, chronic inflammation may result in reduced corneal sensation and decreased reflex activity, leading to increased evaporation and tear film instability. Inflammation can also result in goblet cell loss and decreased mucin production, which further contributes to tear film instability (Table 7).[1]

Table 7. Ocular damage produced by chronic ocular surface inflammation in DED

Reduced goblet cell density and altered corneal epithelial mucin
Squamous conjunctival metaplasia
Reduced corneal sensitivity
Corneal epithelial barrier dysfunction
Detachment of epithelial cells and epithelial cell death

5.1 Ocular surface inflammation and disease severity

Inflammation is a central feature of ocular surface disease. However, this does not necessarily manifest as 'red eyes'.[10] A number of inflammatory markers are detected on the ocular surface of patients with DED, highlighting an active immune-inflammatory reaction (Table 8).

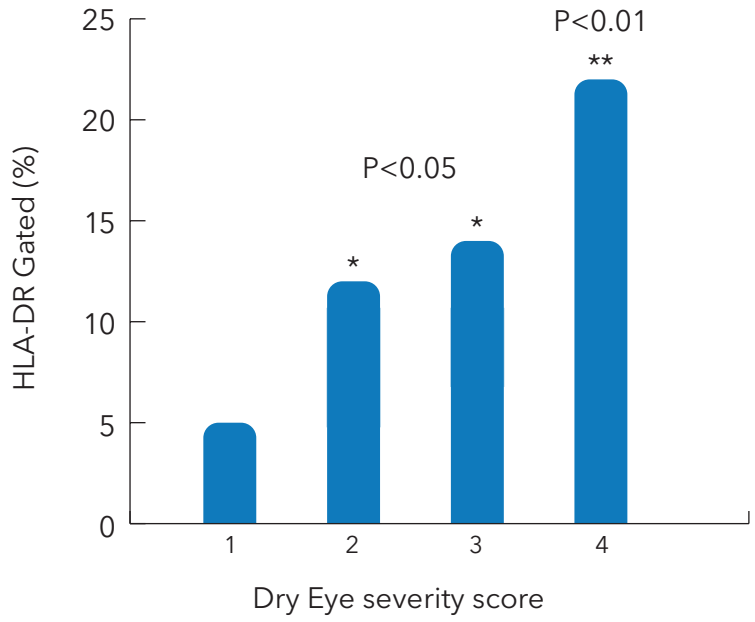
Table 8. Markers of ocular surface inflammation in DED

Increased expression of HLA-DR
Increased expression of cytokines and chemokines
Increased expression of MMPs

Major histocompatibility complex (MHC) class II

The expression of various cell-associated immunomodulatory molecules is increased in DED. The ocular surface of patients with Dry Eye was shown to contain elevated levels of HLA-DR[37] which are correlated with the disease severity (Figure 6).[38] HLA-DR is a major histocompatibility complex (MHC) class II cell surface receptor involved in antigen presentation, and is normally expressed on immune-competent cells, such as monocyte/macrophages and T lymphocytes, and some non-immune cells, such as epithelial cells, dendritic cells and Langerhans cells. Increased expression of HLA-DR also suggests that antigen (presumably autoantigen) presentation occurs efficiently in DED.[9]

Figure 6. HLA-DR expression and severity of DED



The relative expression of HLA-DR antigen in conjunctival cells collected by impression cytology according to Dry Eye severity per the DEWS classification (*P< 0.05, **P< 0.01).[38]

Cytokines and chemokines

Cytokines and chemokines are signalling molecules that mediate intercellular communication. They are produced at the ocular surface by a variety of cells (including epithelial cells and immune cells) and play an essential role in maintaining homeostasis.[39] Clinical studies consistently report elevated levels of various cytokines in tears and conjunctival epithelium of patients with DED. Induction of these cytokines is considered as a hallmark of ocular inflammation.[2,9]

Additionally, correlations between inflammatory molecules and clinical data suggest that inflammation can be responsible for some of the clinical symptoms and signs.[40] Increased levels of several inflammatory cytokines have been correlated with clinical parameters, both in Aqueous-Deficient DED and in Evaporative-related DED.[41]

Lam *et al* reported significant differences in the concentrations of certain cytokines and chemokines in eyes of patients with dysfunctional tear syndrome (DTS) (defined as ocular irritation and at least one objective sign) compared to a symptomatic control eyes. Clinical severity parameters of DTS, such as irritation symptoms, Schirmer test scores and corneal and conjunctival dye staining scores showed a significant correlation with the concentration of cytokines in tears. In this study, subjective signs (severity of irritation) were only correlated to IL-6 levels and corneal and conjunctival staining with IFN-γ, IL-8, MIP-1α, IL-1α, IL-1β and IL-6.[42]

In another study, several cytokines and chemokines were increased in tears of patients with evaporative DED due to meibomian gland disease.[41] These patients had mild to moderate ocular surface signs with moderate to severe symptoms. IL-1 receptor antagonist (IL-1Ra), IL-6, IL-8, and epidermal growth factor (EGF) were significantly correlated with ocular pain and clinical parameters measuring tear stability, tear production or ocular surface integrity.[41] Overall, this study suggests that inflammation plays a role not only in severe or Aqueous-Deficient DED, but also in mild to moderate evaporative DED due to MGD. This is consistent with Lam *et al*, who mentioned that elevated tear cytokines may be a more sensitive disease marker than traditional signs of Dry Eye in patients with mild disease who complain of ocular irritation symptoms.[42]

In addition, one study of 30 healthy volunteers found a significant positive correlation between inflammatory cytokine levels (IL-1α, IL-1β, IL-6, Il-8, and TNF-α) and increased tear osmolarity,[43] which is consistent with the role of tear film instability and hyperosmolarity in the initiation and maintenance of inflammation at the ocular surface.

Factors associated with inflammatory pain, including neuropeptides, proinflammatory cytokines, ganglioside-specific antibodies, and infiltrating inflammatory cells are well documented during Dry Eye.[19] Some inflammatory

cytokines found in tears of patients with DED (i.e. IL-1, TNF-α, IL-6, IL-8, and fractalkine) are known to stimulate the nerve endings that mediate pain and itching. Thus, the presence of these inflammatory mediators in the tears probably accounts for the burning and itching experienced by patients.[41]

Metalloproteinases

Metalloproteinases are endopeptidases that can degrade all classes of extracellular matrix proteins, and are involved in tissue remodelling.[44] Elevated levels and increased activity of MMP-9 have been found in tear fluid of Dry Eye patients.[9] Additionally, in healthy subjects, MMPs are significantly correlated with elevated tear osmolarity[43] and their role in corneal dysfunction associated with Dry Eye Disease has been confirmed in animal models.[45]

5.2 Mechanisms of immune inflammation in Dry Eye Disease

Factors that adversely affect tear film stability and osmolarity can induce ocular surface damages and initiate an inflammatory cascade (Table 9) that generates innate and adaptive immune responses.[9]

Table 9. Ocular surface damage and inflammatory events

Ocular stress leading to tear film instability and increased osmolarity
Activation of antigen-presenting cells (APC)
Apoptosis of resident cells and release of inflammatory mediators
Infiltration of T lymphocytes from draining lymph nodes
Release of key cytokines, including INF-γ, and IL-17 and MMPs
Corneal and conjunctival damages, including goblet cells loss, and neural sensitivity

Ocular inflammation may be considered as both a cause and a consequence of DED. The current proposed mechanism (primarily based on Dry Eye animal models) of the immune reaction leading from repeated desiccating stress to ocular surface damages involved a complex interaction of inflammatory and immune cells, leading to a self-perpetuating (vicious) cycle of inflammation (Figure 2).[11]

Recent studies have shown that Dry Eye Disease is an inflammatory disease with many features in common with autoimmune disease. The current hypothesis is that the relationship between DED and inflammation is not innate or adaptive immunity (autoimmunity) per se, but an abnormal inflammatory cycle sustained by dysregulation of immunity.[19,46]

Innate immune inflammatory response in DED (Table 10)

Ocular surface inflammation in Dry Eye patients likely starts with acute innate immune episodes in response to environmental and/or microbial stress leading to tear film instability and hyperosmolarity of the tear film.[46] Decreased production of aqueous tears or increased tear evaporation result in changes in tear composition that promote inflammation on the ocular surface and lid margin.[47]

The response of cells to ocular surface stress and tear film hyperosmolarity is partly mediated by mitogen-activated protein (MAP) kinases (e.g. c-jun N-terminal kinase, JNK) and NFκB, which play a central role in initiating and maintaining the inflammatory reaction (Figure 7).[24,31] MAP kinases have been identified in the tear film of patients with Dry Eye Disease and promote the transcription of stress-related genes, including inflammatory cytokines (IL-1, IL-6, TNF-α), MMPs, and pro-apoptotic factors.[24,31] Apoptosis of ocular surface cells in DED can be induced by intrinsic (stress-associated MAP kinase) and extrinsic (i.e. tumour necrosis factor and Fas/Fas ligand) pathways.[9]

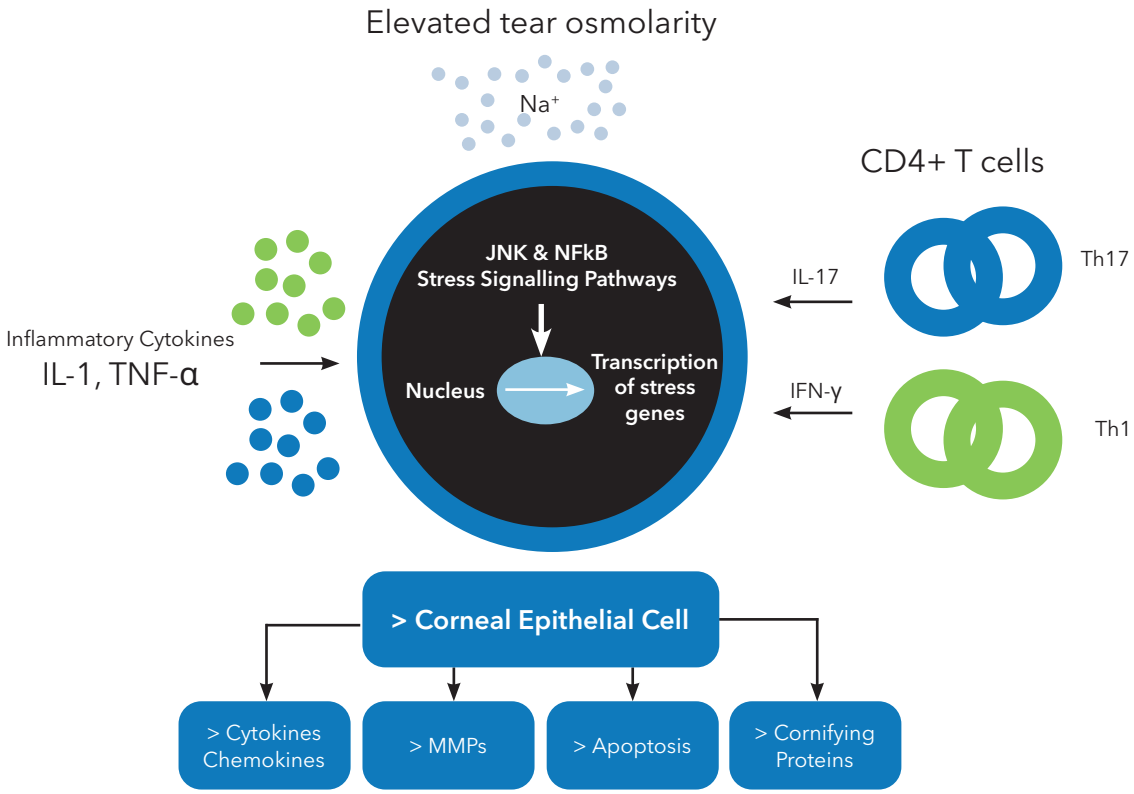
Apoptosis is a process of controlled cell death that can be used to eliminate injured or damaged cells. In the context of immune diseases, apoptosis produced cell debris such as DNA and/or RNA fragments which likely induce autoantigen, and subsequent inflammation.[48] The DNA and/or RNA from apoptotic cells also have the ability to activate toll-like receptors (TLRs), which have been shown to be activated in Sjögren's syndrome.[48]

Inflammatory mediators promote the activation and maturation of immature antigen-presenting cells (APCs). Resident APCs (i.e. ocular epithelial cells, dendritic cells, natural killer cells, monocytes, Langerhans cells, and T lymphocytes) express HLA-DR antigens and TLRs.[2,46] Activation and maturation of APCs lead to the release of a variety of inflammatory mediators (including cytokines, chemokines, MMPs, phospholipases, and the adhesion molecule ICAM-1) that further magnify the innate inflammatory responses. Subsequently, the mature APCs migrate into regional lymph nodes, where they initiate an adaptive immune reaction.[46]

Table 10. Innate immune inflammatory response in DED

Cell desiccation produced by hyperosmolarity
Activation of cellular mitogen-activated protein (MAP) kinases and transcription of stress genes
Increased epithelial cell apoptosis
Release of inflammatory cytokines and metalloproteinases (MMPs) by resident cells
Migration of the APCs to the draining lymph node

Figure 7. Model of immune inflammatory reaction and corneal epithelial disease



Tear dysfunction related alterations in tear composition, including increased osmolarity and inflammatory cytokines produced by epithelial cells (IL-1 and TNF-α) and activated CD4+ T cells (IFN-γ and IL-17) activate the c-jun N-terminal kinase (JNK) and nuclear factor kappa B (NFκB) stress signalling pathways, leading to transcription of stress genes such as inflammatory cytokines and chemokines, matrix metalloproteinases (MMPs), pro-apoptotic factors and cornified envelope precursor proteins.[24]

Adaptive immune inflammatory response in DED (Table 11)

In lymphoid nodes, the APCs promote the infiltration of immune cells in the ocular surface.[46] There is growing evidence from human and experimental studies that ocular surface inflammation in DED is mediated by T helper lymphocytes.[32,45,47] Two subtypes of CD4+ T cells, Th1 and Th17, are thought to function concurrently in DED. The presence of CXCR3 and CCR5 in tears of DED patients is the signature of the Th1 cells infiltration and activation at the ocular surface. These cells promote conjunctival squamous metaplasia and induction of apoptosis of conjunctival cells via the generation of INF-γ.[41,47,48] Th17 cells produce IL-17, which stimulates the production of MMP-3 and MMP-9, leading to further damages of the ocular surface and progression in a chronic cycle of inflammation.[46]

In addition to the development of the inflammatory reaction, immunosuppressive reactions mediated by Th2 lymphocytes and the generation of IL-4 and IL-13 are depressed.[47]

The contribution of B lymphocytes has been also hypothesised, through the recognition and internalisation of a putative Dry Eye autoantigen, self-antigen presentation, cellular interaction with T helper lymphocytes, and B cell differentiation in autoantibody-secreting plasmocytes, leading to further tissue damage.[19]

Table 11. Adaptive immune inflammatory response in DED

Infiltration of T helper lymphocytes (Th1 and Th17)
Infiltration of autoantibody-secreting B lymphocytes
Release of various cytokines, including INF-γ and IL-17
Infiltration of B lymphocytes and differentiation in cell-secreting antibodies
Activation and maturation of antigen-presenting cells (APCs)
Activation of lymphangiogenesis

INF-γ and IL-17 and ocular surface damages

Increased concentrations of interferon-gamma (INF-γ) in tears of patients with DED have been reported.[47] INF-γ is a pleiotropic cytokine involved in a variety of immune functions, including recruitment of naïve CD4+ cells. INF-γ also increases the expression of HLA class I and HLA class II antigens in epithelial cells and

stimulates T cells to proliferate, thus, perpetuating the immune cascade. This cytokine is also involved in goblet cell loss and epithelial cell apoptosis.[45,47]

In addition, INF-γ was also shown to antagonise the IL-13 signalling, leading to decrease goblet cell density in a mouse model.[47] IL-13 has been found in human tears and is a modulator of goblet cell density in the conjunctival epithelium.[47] This observation is consistent with the correlation between severity of ocular surface epithelial disease (assessed by corneal and conjunctival staining) in DED and INF-γ levels in tears.[42]

IL-17 has been detected in tears of patients with severe autoimmune Dry Eye condition associated with Sjögren's syndrome. It can promote the activation of MMP-9, which was found to be associated with increased fluorescein permeability, punctate epithelial erosions and corneal surface irregularity in DED.[45,47] MMP-9 is certainly responsible for proteolytic degradation of tight junction that maintain the apical corneal epithelial barrier function.[24,47] Corneal barrier dysfunction by MMP-9 may then facilitate increased infiltration of other immune cells in the conjunctiva, thus perpetuating the inflammatory reaction.

5.3 Anti-inflammatory therapy for Dry Eye Disease

The outcomes of ocular inflammation can be dangerous for the eye and vision. Uncontrolled inflammation may result in thinning or melting of altered ocular tissues and subsequent scarring with irreversible changes that could lead to vision loss.

Even with only moderate Dry Eye, there is an inflammatory reaction (often subclinical) of the ocular surface and the lacrimal glands.[9,19,49] To break the vicious cycle of surface damage and inflammation, anti-inflammatory treatments are recommended in patients with moderate to severe Dry Eye Disease.[10,18,19]

Anti-inflammatory therapies, including corticosteroids, are recommended by the DEWS II for treatment of Dry Eye Diseases.[20]

There is currently a limited range of topically applied agents available to reduce inflammation and restore normal tear film:[9]

- Topical CsA significantly reduced severity of corneal fluorescein staining after 4 to 6 months of treatment.[50] Although CsA improves tear production in patients with ocular inflammation associated with Dry Eye, relief of signs and symptoms is often delayed by 1 to 6 months from the initiation of therapy, and it has been reported that 20% of patients treated with Cyclosporine experience burning and stinging[51]

- Topical corticosteroids are one of the most potent topically applied anti-inflammatory drugs to treat ocular inflammation. They can effectively and rapidly (within 2-4 weeks in most cases) relieve the symptoms and signs of moderate or severe Dry Eye. They must be adjusted to match severity of symptoms, and tapered appropriately. They can be administered concurrently with CsA. Due to potential risk of side effects, long-term use of corticosteroids should be avoided[10]
- Tetracycline derivatives: These possess antibacterial and anti-inflammatory properties. However, despite extensive evidence from experimental trials indicating the potential benefits of their administration in the treatment of DED, there is limited clinical trial evidence of their efficacy[9]

Section 6:

Corticosteroids in Dry Eye Disease

Corticosteroids have an important place in the therapeutic strategy for ocular inflammation. These drugs constitute the most effective means of treating inflammations and diseases caused by immune reactions, both in general medicine and in ophthalmology.

Topical corticosteroids act through several mechanisms to reduce ocular inflammation. As reviewed recently,[32] corticosteroids function via suppression of cellular infiltration, capillary dilation, proliferation of fibroblasts, and collagen deposition. They stabilise intracellular and extracellular membranes. Corticosteroids increase the synthesis of lipocortins that block phospholipase A2 and inhibit histamine synthesis in mast cells. Inhibition of phospholipase A2, an essential step in the inflammatory cascade, prevents the conversion of phospholipids to arachidonic acid. Corticosteroids also interfere with transcription factor NFκB, which regulates the synthesis of a number of pro-inflammatory molecules, thereby stimulating lymphocyte apoptosis.

Corticosteroids mediate their anti-inflammatory effects primarily through modulation of the cytosolic glucocorticoid receptor (GR) at the genomic level. After corticosteroids bind to the GR in the cytoplasm, the activated corticosteroid-GR complex migrates to the nucleus, where it upregulates the expression of anti-inflammatory proteins and represses the expression of pro-inflammatory proteins. However, recent work suggests that the activated corticosteroid-GR complex also elicits non-genomic effects, such as inhibition of vasodilation, vascular permeability and migration of leukocytes.

Table 12. Main anti-inflammatory activity of corticosteroids

Gene regulation of inflammatory mediators (cytokines)
Phospholipase A2 inhibition
Inhibition of vascular permeability

Topical corticosteroids are a valuable tool in the management of Dry Eye.[52] While no steroid related complications were observed in short-term clinical trials, there is a potential for toxicity over the long-term use, such as increased intraocular pressure (IOP) and cataracts (Table 13). Most guidelines recommend that their use be limited to more severe disease that is not controlled by other treatments (artificial tears substitutes, gels/ointments, moisture chamber spectacles) and that these agents be used in pulse therapy for as short a duration as possible.[18,53] The propensity of topical corticosteroids to induce adverse effects depends, in part, on their structure, potency, dose and duration of treatment.[53,54]

This may limit the use of more potent steroids for chronic therapy of Dry Eye. It was suggested that the risk-benefit ratio is better with soft steroids such as Fluorometholone and Loteprednol etabonate that have less intraocular activity and a lower likelihood of raising IOP.[45,52]

Table 13. Potential side-effects of topical corticosteroid when used in the long-term

Intraocular pressure elevation, with possible development of glaucoma and optic nerve damage
Posterior subcapsular cataract
Delayed wound healing
Lower resistance to infection

6.1 Experience with potent corticosteroid eye drops

Dexamethasone 0.1% is used for moderate to severe ocular inflammation. It has the greatest potential to affect intraocular pressure (see Table 14 , page 40), and ideally should be used for short courses only and not for chronic inflammation.

Topical 1% Prednisolone acetate is one of the most commonly used topical steroids and is one of the most clinically potent. It is highly effective in DED, but is limited to short-term use (2-4 weeks) due to side effects. Topical steroids are used to control episodes of exacerbation and as an adjunct therapy to other treatments, such as CsA.[55,56]

In clinical studies, 1% Prednisolone acetate was shown to be effective in patients with moderate to severe DED, and treatments up to 8 weeks were shown to be safe. In Sjögren's syndrome, patients (N=21) with moderate to severe Dry Eye, treatment with topical 1% Methylprednisolone given 3 to 4 times daily for several weeks

(up to 12 months) improved clinical outcomes (corneal and conjunctival staining). After 2 weeks of treatment, symptoms regressed moderately (in 43% of cases) or completely (57%) and no complications were observed. Complications of corticosteroid therapy in patients receiving prolonged therapy included increased IOP in one patient at 3 months, worsening of pre-existing posterior subcapsular cataract in one patient at 6 months, and formation of posterior subcapsular cataract in another patient at 6 months.[55]

In another study using 1% Methylprednisolone in 53 patients with Sjögren's syndrome, DED was performed to determine the recurrence rate after Methylprednisolone therapy. Initial therapy consisted of eye drops 4 times a day for 2 weeks, and then patients were re-evaluated and tapered off the medication every 2 weeks, until discontinuation. A significant reduction ($P<0.001$) in subjective symptoms and fluorescein staining, and an improvement in TFBUT and Schirmer test were observed after treatment. After the first pulse therapy, the mean survival was 57 weeks and 11 (20.8%) patients recurred. After the second pulse therapy, mean survival was 72 weeks and only 1 patient recurred. No serious complications, including IOP elevation and cataract formation, were encountered during the entire follow-up period.[57]

6.2 Experience with soft corticosteroid eye drops

The safety limitation of topical corticosteroids has led to the proposal of soft corticosteroids in the treatment of DED. The risk-benefit ratio may be better with soft steroids because they have less intraocular activity and a lower likelihood of raising IOP.[45,52]

Section 7:

Benefits of preservative-free eye drops

Many of the corticosteroids currently on the market contain preservatives, which are used in ophthalmic preparations to prevent microbial proliferation. Their cytotoxic effect on bacteria cannot be achieved without a minimum toxicity for tissues where they are applied.[36]

Quaternary ammoniums, including benzalkonium chloride (BAK), are probably the most cytotoxic preservatives used in eye drops (Table 14). They induce a destabilisation of the lacrimal film by rupture of the lipid component. This leads to accumulative evaporation of tears, worsening the Dry Eye condition.[36] They also promote apoptosis at the ocular surface, even at low concentrations, whereas a necrotic process appeared at higher concentrations. Superoxide anions may play an important role in tissue damage induced by preservatives in ocular surface disorders.[58] They are known to stimulate the generation of proinflammatory mediators at the ocular surface, causing epithelial damages and a decrease in mucin.[36] The presence of preservatives in the formulation of ophthalmic preparations can also be a source of unfavourable compliance because of side effects.[59] Unpreserved topical eye drops are thus one option to totally eliminate the toxicity associated with preservatives.[36]

As mentioned in the TFOS DEWS II, preservative-free drops may be a better choice for patients who have pre-existing ocular surface conditions and/or need frequent instillation of eye drops.[20]

In a randomised, parallel-group, case-control study, the efficacy of preservative-free 0.1% hyaluronic acid and 0.1% Fluorometholone combined with 0.05% Cyclosporine was compared with the efficacy of preserved 0.1% HA and 0.1% Fluorometholone combined with 0.05% Cyclosporine, in treating DED.[60] The preservative-free eye drops improved subjective symptoms, TBUT, Schirmer score and impression cytology findings more than preserved eye drops.

Similarly, a retrospective review of 31 patients treated with preservative-free 0.01% topical Dexamethasone showed a significant subjective improvement in symptoms in 84% of the subjects with chronic ocular surface irritation, and/or tearing, refractory to various preserved topical steroids, including 0.2% Loteprednol, 0.1% Fluorometholone and 1% Prednisolone.[61]

Table 14. Dose-dependent toxicity of benzalkonium chloride on the ocular surface

BAK concentration	Ocular effects
0.004%	Significant reduction of the lacrimal tear film
0.005%	Direct toxicity on superficial cells with epithelial erosion
0.007%	In-vitro conjunctival epithelial cell lysis in 90-100 sec
0.01 %	Important epithelium alteration, stimulation of limbal and conjunctival infiltration of inflammatory cells
0.02%	Corneal cicatrisation delay
0.1%	Destruction of the endothelium and irreversible corneal oedema in case of intracameral injection
0.1 to 0.5%	Major toxic keratitis, epithelial metaplasia, corneal infiltration of inflammatory cells, and neovascularisation induced by repeated administration in rats
1 to 2% (in animals)	Total destruction of the anterior segment (conjunctiva and cornea) in less than one week

Adapted from Vaede D, et al. J Fr Ophthalmol. 2010.[62]

In humans, the risk of BAK toxicity is potentiated by contact lens wear, particularly HEMA (2-Hydroxyethyl Methacrylate) contact lens wear, to which BAK can bind with high affinity.

Section 8:

Conclusion

Dry Eye Disease is a highly prevalent disease of the tear film. Although ocular symptoms are mild to moderate in most cases, chronic ocular irritation or discomfort may impact visual function, daily activities, social and physical functioning, workplace productivity, and overall quality of life.

Dry Eye Disease regarded as a chronic inflammatory disease involving infiltration and activation of immune cells, and the generation of inflammatory mediators with subsequent ocular surface damages.

Although artificial tear substitutes or other ocular lubricants are effective in mild cases to control signs and symptoms, these treatments are not sufficient to counteract the underlying mechanisms of the disease. The sustained inflammatory reaction at the ocular surface of patients with Dry Eye Disease justifies the use of anti-inflammatory treatments.

Section 9:

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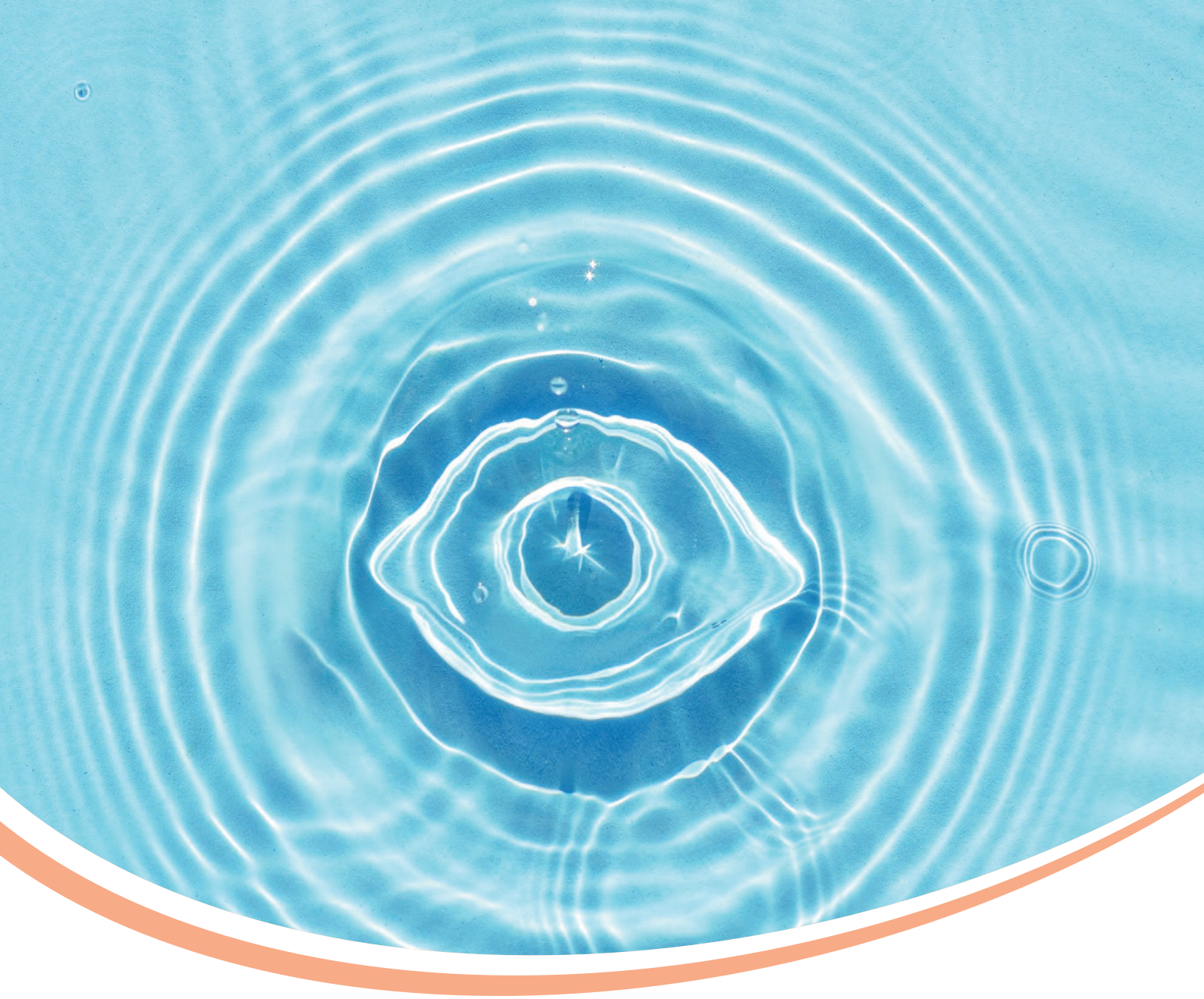
Notes



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