

Allergy & Dry Eye



INTERLINKED
ELEMENTS OF

INTERLINKED ELEMENTS OF OCULAR ALLERGY AND DRYNESS



Pr. Kostas BOBORIDIS MD, PhD, FEBO

Assistant Professor in Ophthalmology

Oculoplastic and Ocular Surface Disease

Aristotle University of Thessaloniki, Greece

Dr. Nikolaos V. KOZEIS MD, PhD1, PhD2, FICO, FEBO, MRCOphth

Eye Surgeon - Paediatric Ophthalmologist

Director of Paediatric Eye & Strabismus Department

‘Ophthalmica’ Eye Institute, Thessaloniki, Greece

Vis. Professor of Ophthalmology, University Hospitals, Cleveland, Ohio, USA

Dr. Serge DOAN MD

Department of Ophthalmology, Bichat Hospital and foundation A. de Rothschild, Paris, France



CONTENT

1

PATHOPHYSIOLOGY & CLINICAL PRESENTATION OF OCULAR SURFACE DISEASE

9

OCULAR ALLERGY	10
Seasonal Allergic Conjunctivitis	11
Perennial Allergic Conjunctivitis	11
Vernal Keratoconjunctivitis (VKC)	12
Giant Papillary Conjunctivitis (GPC)	12
Atopic keratoconjunctivitis (AKC)	13
Ocular toxicity - Drug related allergy	13
Clinical presentation of Contact Allergy	15

OCULAR SURFACE DISEASE: THE VICIOUS CYCLE OF DRY EYE DISEASE AND SURFACE INFLAMMATION	16
Meibomian gland dysfunction (MGD)	16
ALLERGY, A SOURCE OF DRYNESS	18
Loss of natural protection from allergens	18
Allergy, tear film and ocular surface: what the biology tells us?	19
Dry eye disease interlinks with allergic reaction	20
Allergic conjunctivitis and Dry Eye Disease in children	21

2

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS OF DED & ALLERGY

25

HISTORY-TAKING	26
Allergy Evaluation	26
DED - OSD Evaluation	26
CLINICAL EXAMINATION	28
Signs of allergy	28
Signs of DED	29
The non-specific signs that could be associated with allergy or dryness	29
OVERVIEW OF CAUSATIVE FACTORS	30
ADDITIONAL EXAMINATION TESTS	32
Medical / allergist assessment	32
Ophthalmologist assessment	32

3

STRATEGY FOR OCULAR ALLERGY MANAGEMENT

37

GENERAL CONSIDERATION OF OCULAR ALLERGY AND DED MANAGEMENT	38
GENERAL MANAGEMENT: PRIMARY MEASURES, LIFESTYLE INTERVENTIONS AND ELIMINATION OF EXACERBATING FACTORS	39
GENERAL MANAGEMENT OF OCULAR ALLERGY AND OSD	40
FOCUSED MANAGEMENT OF OCULAR ALLERGY	42
Management of mild to moderate Seasonal & Perennial Allergic Conjunctivitis	42
Management of moderate to severe Seasonal and Perennial Allergic Conjunctivitis	45
Conclusion	49
References	50



1

PATHOPHYSIOLOGY & CLINICAL PRESENTATION OF OCULAR SURFACE DISEASE

.1 OCULAR ALLERGY

An ophthalmologist encounters cases of ocular allergies almost on a daily basis. According to the World Allergy Organization, approximately 20% of the population in developed countries is affected by some form of allergy, with an increasing rate year by year.

Forty to sixty per cent of the patients with common types of allergic conjunctivitis, like Seasonal Allergic Conjunctivitis (SAC) and Perennial Allergic Conjunctivitis (PAC), present with ocular symptoms, only while the rest might also have symptoms of allergic rhinitis.

Chronic cases of ocular allergies, like Vernal and Atopic Keratoconjunctivitis (VKC and AKC) are not easily distinguishable from non-allergic conditions like Contact Dermatoconjunctivitis (CDC) and Giant Papillae Conjunctivitis (GPC), since they all present with similar symptoms. Table 1 presents the main features of the above-mentioned conditions.

This brochure focuses on the most common types of ocular allergies, SAC and PAC, their relationship to ocular surface dryness, their diagnosis and management.

Ref (1-3)	Triggering factors	Period	Population	Characteristics	Mediator
SAC	Pollen	Spring	Children and adolescents, atopic adults	Hyperemia, itching, tearing, edema, drying	IgE
PAC	House dust mites, animal dander, molds	Perennial	Children and adolescents, atopic adults	Hyperemia, itching, tearing, edema, drying	IgE
VKC	Pollen	Spring	Young males in warm climates	Goblet cells increase inducing excess mucus	IgE & T _h cells
AKC	Atopic status, MGD	Chronic	Young adults	Loss of Goblet cells, drying	IgE & T _h cells
CDC	Cosmetics, contact lens solutions and eye drops	Intermittent	Everybody	May affect non-allergic patients	Non-allergic
GPC	Mechanical friction with exogenous materials (lenses, sutures etc.)	Acute	Everybody	Giant papillae	Allergic & non-allergic

Table 1: Main features of ocular allergies

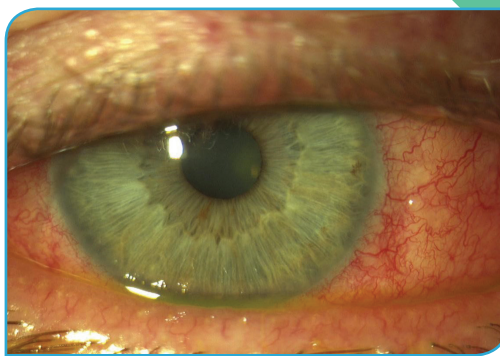
Seasonal Allergic Conjunctivitis⁽¹⁻³⁾

Seasonal Allergic Conjunctivitis (SAC) is the most frequent form of ocular allergy. The majority of patients just suffer a few mild episodes annually, but approximately 30% of the allergic patients suffer frequent intense episodes with persistent symptoms⁽⁴⁾. The most common allergens causing SAC are pollen from trees, grass and weeds, and the clinical manifestations follow a periodic pattern, appearing mostly during the spring and summer time. The intensity of symptoms such as itching, tearing, redness foreign body sensation and photophobia varies widely, and in some severe cases, they may limit or even restrict the daily activities.

SAC is an ocular allergy which presents with mild to moderate symptoms and signs, mainly involving the palpebral conjunctiva and almost never the cornea, unless in rare, severe cases, leading to a sight-threatening condition.

SAC is a common, often under-diagnosed and under-treated condition, and when accompanied by allergic rhinitis, the burden of the disease is increased even more, diminishing the patient's quality of life.

Clinical presentation of SAC

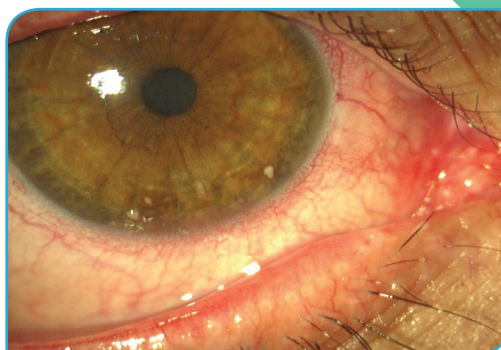


Pict. 1.1. Clinical presentation of SAC. Diffuse conjunctival hyperemia, chemosis and epiphora. Note there is no corneal involvement. Picture Courtesy of Prof. Boboridis.

Perennial Allergic Conjunctivitis⁽¹⁻³⁾

Perennial Allergic Conjunctivitis (PAC) symptoms are the same as in SAC but they last during the whole year. In both conditions (SAC and PAC), the symptoms first occur during childhood and young adulthood. Common allergens include animal dander, dust and dust mites, moulds, cosmetics and other chemical irritants. PAC shares the same pathophysiology (discussed in section 1.3) and management patterns (discussed in Chapter 3) with SAC.

Clinical presentation of PAC



Pict. 1.2. Clinical presentation of PAC. Similar features as in SAC. Signs of conjunctival redness and chemosis may be less obvious than in acute seasonal cases. Picture Courtesy of Prof. Boboridis.

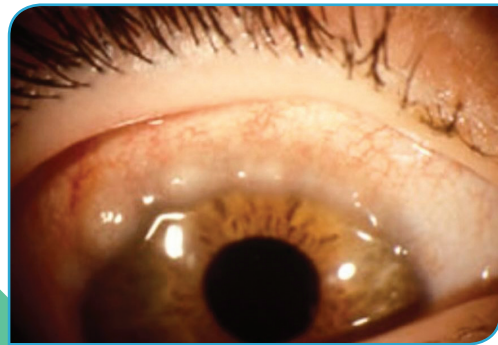
Vernal Keratoconjunctivitis (VKC)⁽⁵⁾

Vernal Keratoconjunctivitis (VKC) manifestations also follow a seasonal pattern, mainly from April to September depending on the geographical location⁽⁵⁾ and are characterized by inflammation of the conjunctiva. The disease is associated with warm and humid climates and mostly affects boys and young men between the ages of 4 and 20.

Clinical presentation of VKC



Pict. 1.3. Clinical Presentation of VKC. Characteristic vernal plaque or shield ulcer on paracentral corneal involvement in VKC. Picture Courtesy of Prof. Boboridis.

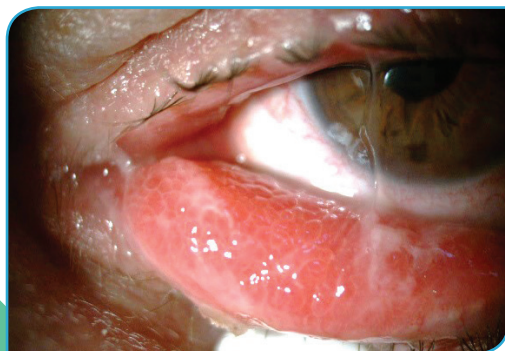


Pict. 1.4. Limbal form of VKC with the characteristic small white-yellow chalky eosinophilic concretions along the corneoscleral limbus called Horner-Trantas dots.

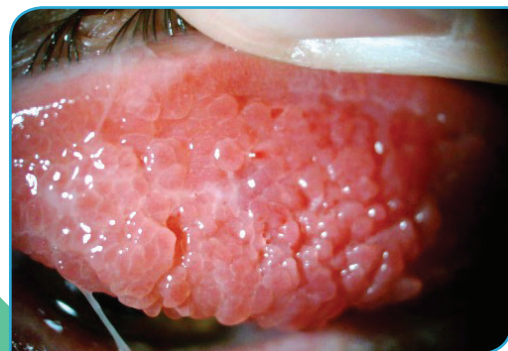
Giant Papillary Conjunctivitis (GPC)⁽¹⁻³⁾

Giant Papillary Conjunctivitis (GPC) represents another type of ocular inflammatory reaction with both allergic and non-allergic pathophysiology. It is caused by mechanical irritation of the eye by a foreign body, usually contact lenses or sutures and is characterized by the development of giant papillae along the upper tarsal surface.

Clinical presentation of GPC



Pict. 1.5. Clinical presentation of GPC on lower palpebral conjunctiva. Note watery - mucous discharge and the relatively uninvolved bulbar conjunctiva. Picture Courtesy of Prof. Boboridis.



Pict. 1.6. Clinical presentation of GPC. Characteristic giant papillae of the upper palpebral conjunctiva on GPC. Picture Courtesy of Prof. Boboridis.

Atopic keratoconjunctivitis (AKC)⁽⁶⁾

Atopic keratoconjunctivitis (AKC) is another allergic condition which affects atopic patients. It affects 25-40% of people suffering from atopic dermatitis⁽⁶⁾. AKC pathophysiology is similar to VKC.

Ocular toxicity - Drug related allergy^(7,8)

Ocular toxicity comprises chemical irritation of the ocular tissues, delayed (cell-mediated) hypersensitivity and dose dependent toxic response to a topically applied ophthalmic medication, leading to ocular surface changes.

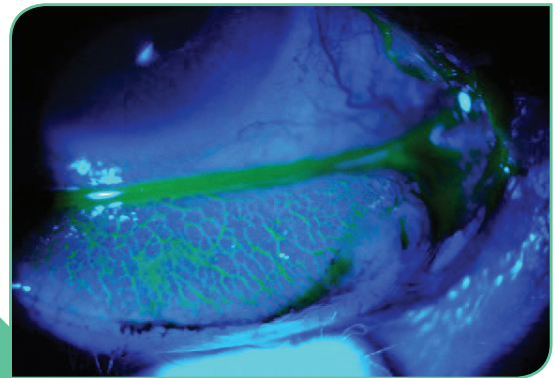
Preservatives such as BAK, a quaternary ammonium molecule, have a strong detergent effect on lipids and cell membranes. BAK is the most commonly used preservative in IOP lowering eye drops. Human corneal and conjunctival cells showed a dose-dependent decrease in cell survival when treated with solutions containing increasing BAK concentrations.

Clinical studies report the detrimental effects of BAK on the tear film and ocular surface. Dry eye, Meibomian gland dysfunction (MGD), conjunctival and corneal epithelial changes are all induced by a documented underlying inflammation process.

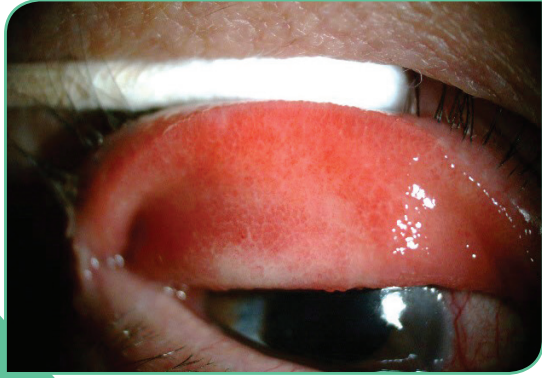
The initial harmful event is related either to an allergic reaction (type I hypersensitivity - early stage of treatment) or a toxic response. Ocular surface toxicity manifests either as true tissue toxicity or delayed cell-mediated hypersensitivity (type IV) which predominantly leads to allergic blepharitis, a condition difficult to differentiate from MGD, skin inflammation or contact dermatitis^(7,8).



Pict. 1.7. Diffuse follicular toxic-allergic response of the lower palpebral conjunctiva due to BAK preserved topical glaucoma medication.
Picture Courtesy of Prof. Boboridis.



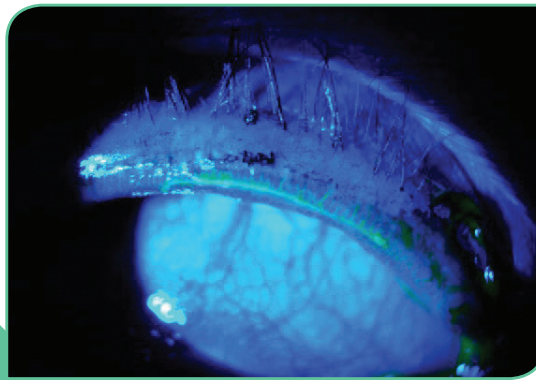
Pict. 1.8. Patient showing the irregular conjunctival surface with fluorescein pooling under blue cobalt illumination.
Picture Courtesy of Prof. Boboridis.



Pict. 1.9. Diffuse follicular response of the upper bulbar conjunctiva in toxic conjunctivitis.
Picture Courtesy of Prof. Boboridis.



Pict. 1.10. Diffuse follicular reaction in toxic conjunctivitis resulting in conjunctival chemosis and reversible functional punctum occlusion due to edema of the conjunctival lining.
Picture Courtesy of Prof. Boboridis.



Pict. 1.11. Patient with fluorescein staining. Intense staining of the inner corner of the upper lid margin reveals lid wiper epitheliopathy as a sequelae from toxic conjunctivitis induced by BAK preserved topical medication.
Picture Courtesy of Prof. Boboridis.

Clinical presentation of Contact Allergy⁽¹⁾

Allergic reactions stemming from the eyelid represent another type of ocular allergy. One such condition is eyelid dermatitis related to atopic dermatitis. It is usually caused by irritants transferred by the hands to the eyelids, leading to red, swollen and itchy eyelids.

Contact dermatitis (CD) is an acute inflammation of the skin most often caused by irritants or allergens. The primary symptom of CD is pruritus. Erythema usually develops and the skin coloration changes to red followed by blistering and ulceration. CD is usually caused by irritants such as plants, soaps, chemicals, and body fluids, comprising 80% of cases, or by allergens, comprising 20% of cases.

Symptoms are often on or near the hands but occurring on any exposed skin surface. Symptoms can include predominantly pain in the cases of irritable CD or pruritus in the case of allergic contact dermatitis.

Diagnosis is by exposure history, examination, and sometimes skin patch testing. Patch testing is helpful when Atopic Contact Dermatitis (ACD) is suspected and the trigger has not been identified.

Treatment entails antipruritics, topical corticosteroids, and avoidance of causes. Moreover, treatments include cool compresses, topical corticosteroids, and systemic antihistamines as needed for pruritus.

Clinical presentation of Contact Allergy



Pict. 1.12. Clinical presentation of eyelid-skin allergy. Acute erythema and swelling of periocular eyelid skin on allergic contact dermatitis.

Picture Courtesy of Prof. Boboridis.



Pict. 1.13. Chronic erythema and swelling of mainly lower eyelid skin due to prolonged topical treatment in glaucoma. Skin fibrosis and shrinkage may result in cicatricial ectropion in chronic cases.

Picture Courtesy of Prof. Boboridis.

2 OCULAR SURFACE DISEASE: THE VICIOUS CYCLE OF DRY EYE DISEASE AND SURFACE INFLAMMATION

Dry eye disease (DED), as defined by the Dry Eye Workshop in 2007⁽⁹⁾ and updated in 2017⁽¹⁰⁾, is “a multifactorial disease of the ocular surface characterized by the loss of homeostasis of the tear film, and accompanied by ocular symptoms. The tear film instability and hyperosmolarity, inflammation, damage, and neurosensory abnormalities play etiological roles”. Tear hyperosmolarity and tear film instability can co-exist and mutually reinforce the vicious cycle of DED progression, maintaining the ocular surface inflammation.

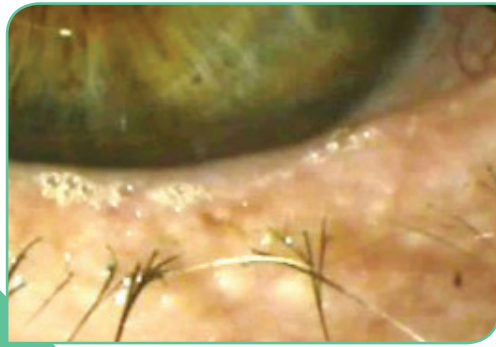
The tear film lubricates the surface of the eye. Its composition is mainly aqueous, but also comprises mucus and lipid, in a specific balance. DED develops either due to abnormal tear composition or/and reduced tear volume.

An abnormal tear film composition or volume may be due to lacrimal glands dysfunction (aqueous-deficient DED) as a result of autoimmune conditions (Sjögren syndrome), non-autoimmune deficiencies (age-related, inflammatory infiltration of the lacrimal glands, obstruction of the lacrimal glands, denervation etc.), or due to increased water evaporation (evaporative DED)⁽⁹⁾. However, in DED, the co-existent deficiencies in both tear quantity and quality, irrespective of the initial cause of tear film instability, hyperosmolarity and inflammation, exacerbate the ocular surface damage⁽¹⁰⁾. That is why in Sjögren syndrome cases (a typically aqueous deficient condition), an evaporative component due to associated meibomian gland dysfunction, also exists⁽¹¹⁾. Thus, aqueous deficient and evaporative dry eye should be perceived as a continuum.

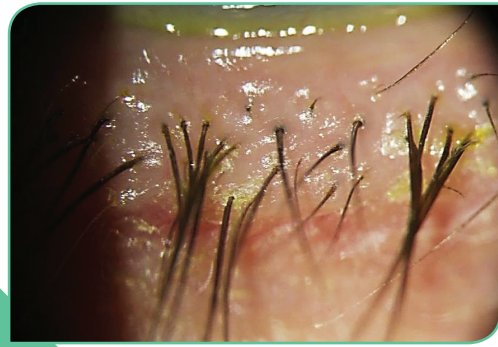
Meibomian gland dysfunction (MGD)

The meibomian glands produce meibum, which prevents the evaporation of aqueous part of the tear film. MGD is a chronic condition, usually characterized by obstruction of the terminal ducts, resulting in low meibum secretion⁽¹⁵⁾.

Meibomian plugs, telangiectasias, hyperhemia and oedema can be observed on the eyelid margin. Meibomian gland testing reveals milky or solid meibum, indicative of MGD. Patients with chronic types of allergic conjunctivitis, PAC in particular, have higher frequency of MGD than control subjects^(16,17). MGD is one of the causes of tear film instability and ocular surface drying, and its treatment is an integral part of the treatment of chronic allergies.



Pict. 1.14. Meibomian foam from saponified meibum on the lid margin represents an early sign of MGD.
Picture Courtesy of Prof. Boboridis.



Pict. 1.15. Biofilm on the eyelid margin skin in-between eyelashes in the form of a dandruff-like material indicates the early inflammatory process leading to MGD.
Picture Courtesy of Prof. Boboridis.

1

1.3 ALLERGY, A SOURCE OF DRYNESS

Loss of natural protection from allergens

Allergy may be the underlying cause of dry eye. Many symptoms of DED including itching, hyperemia and overlacrimation have a periodic pattern of presentation⁽¹⁸⁾. They are more intense during the spring (triggered by pollen, suggesting allergic contribution) and winter (triggered by low humidity, pointing to dryness) and abate during the summer⁽¹⁹⁾. Perennial symptoms are attributed to indoor causes such as dust, mould, pet dander etc⁽¹⁹⁾.

Thus, it has been proposed that ocular allergy is a risk factor for DED⁽²⁰⁾.

On the other hand, tear film instability due to DED leads to less protection of the external ocular surface from its exposure to dust, pollen and other allergens, exacerbating the allergic manifestations.

The tear film is divided into three layers as it is shown in Fig.1.1.

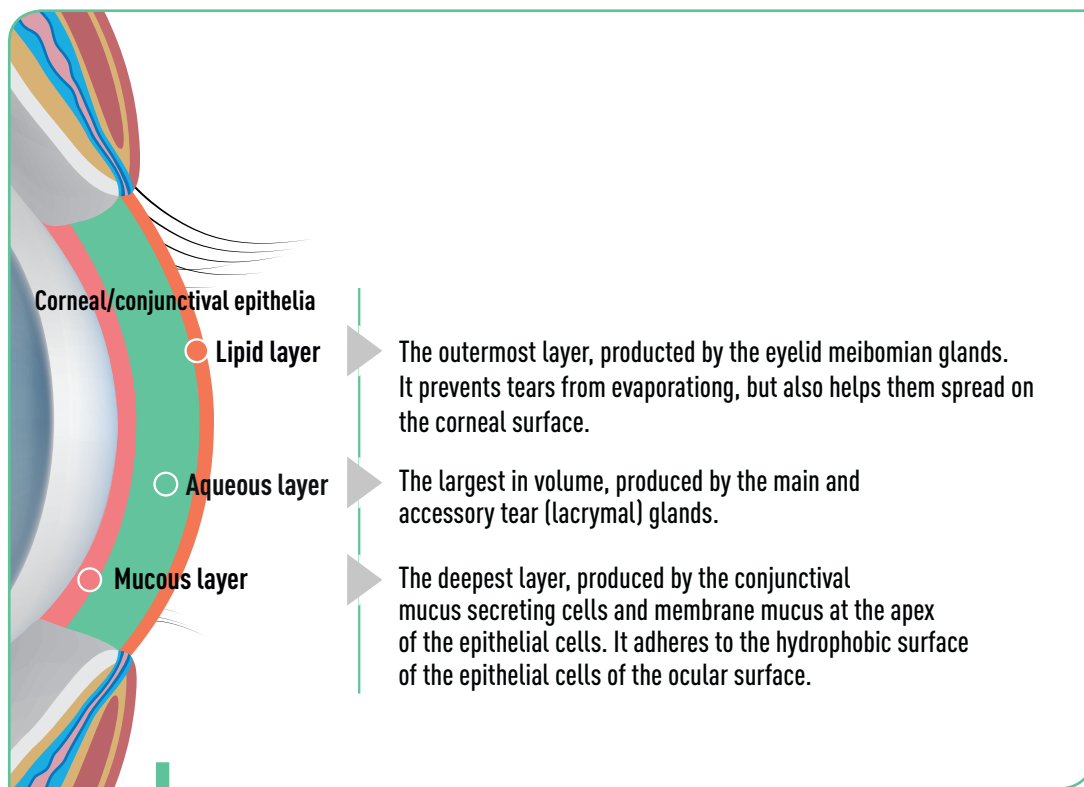


Fig. 1.1. The tear film layers

Allergy, tear film and ocular surface: what does the biology tells us?

In the IgE-mediated types of allergy, IgE production is promoted by the cytokines released by Th2 differentiated T-cells. The cascade of events after initial exposure to allergens is illustrated in Fig. 1.2.

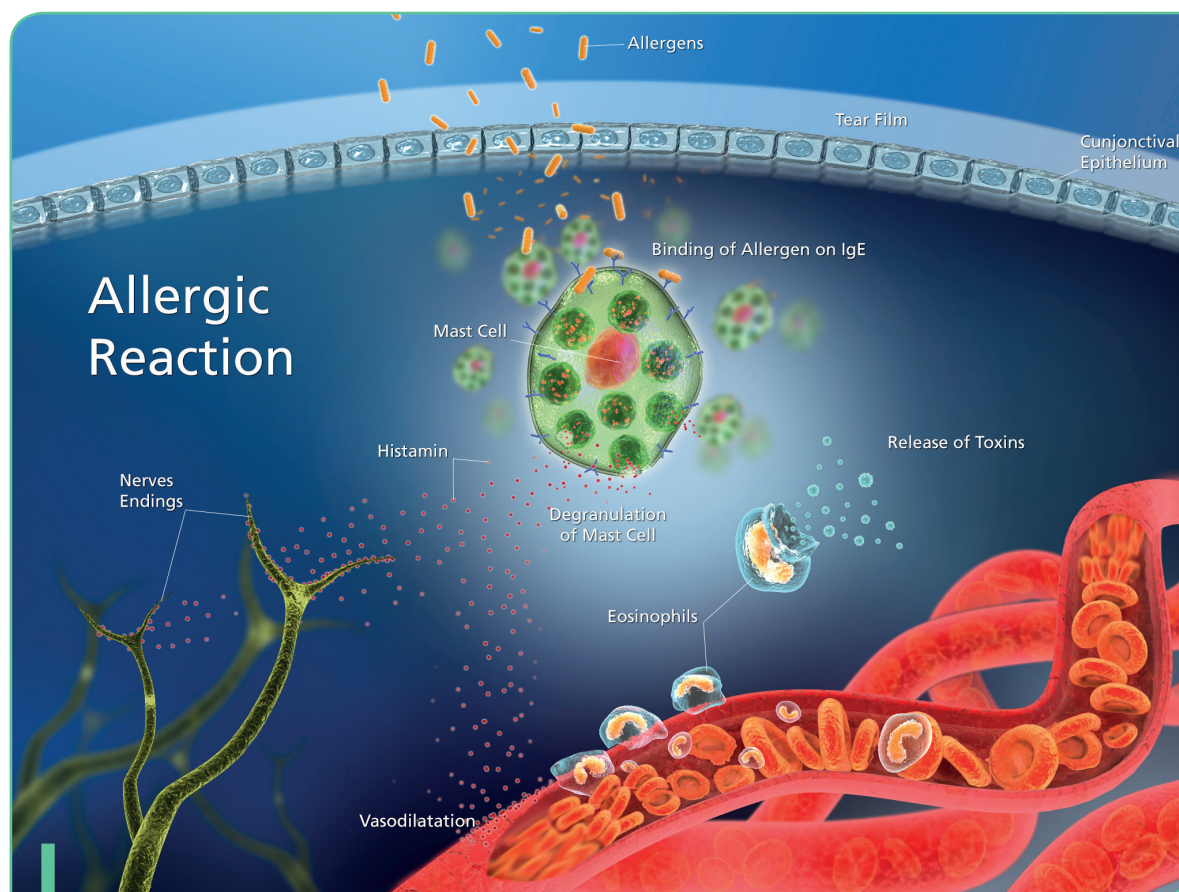


Fig. 1.2. In the IgE-mediated types of allergy, IgE production is promoted by the cytokines released by Th2 differentiated T-cells. Exposure to allergen leads to immediate IgE binding to its receptor on the surface of the sensitized conjunctival mast cells. Degranulation of the mast cells leads to the release of their mediators including histamine and proteolytic enzymes, responsible for the early phase allergic reaction. The complement system proteins may also contribute to the degranulation of the mast cells, as well as to attraction of macrophages and granulocytes. Histamine promotes vasodilation, hyperemia and itching by interacting with the local nerve endings, while the enzymes, possibly activate other proteases involved in the degradation of the extracellular matrix, and infiltration of inflammatory cells during the later phase of the response⁽¹²⁾.

The changes occurring in the tear film composition innitiate with tear hypersmolarity that leads thyper-somotic stress of the undelying epithelia (Fig. 1.3 - 1 & 2). These changes lead to cell damage (Fig 1.3. - 3) followed by cell death via apoptosis (Fig.1.3 -4).

The late phase occurs around 6 hours after the initial tigger. It is associated with the expression and secretion of inflammatory mediators (leukotrienes, prostaglandins, PAF, etc.) by the mast cells, which attract and activate the inflammatory cells (Fig.1.3 - 5), in particular eosinophils and neutrophils. Moreover, histamine also induces the expression of adhesion molecules and the synthesis of proin-flammatory interleukins (IL-6 and IL-8) by the epithelial cells and conjunctival fibroblasts. Th2 derived cytokines attract eosinophils and promote the response to the corneal and the conjunctival epithelia.

Then goblet cells are stimulated and the mucus increases. However, in chronic forms, ocular surface mucins are reduced (Fig. 1.3-6 & 7)⁽²¹⁾. This cascade of events involving disruption of homeostasis, cell death, and inflammation creates a vicious cycles that promotes dryness and exacerbates symptoms.

In conclusion it is becoming more and more evident that ocular allergy and dry eye disease are interlinked regarding their symptoms and their pathophysiology with inflammation playing the central role in both conditions background and progression.

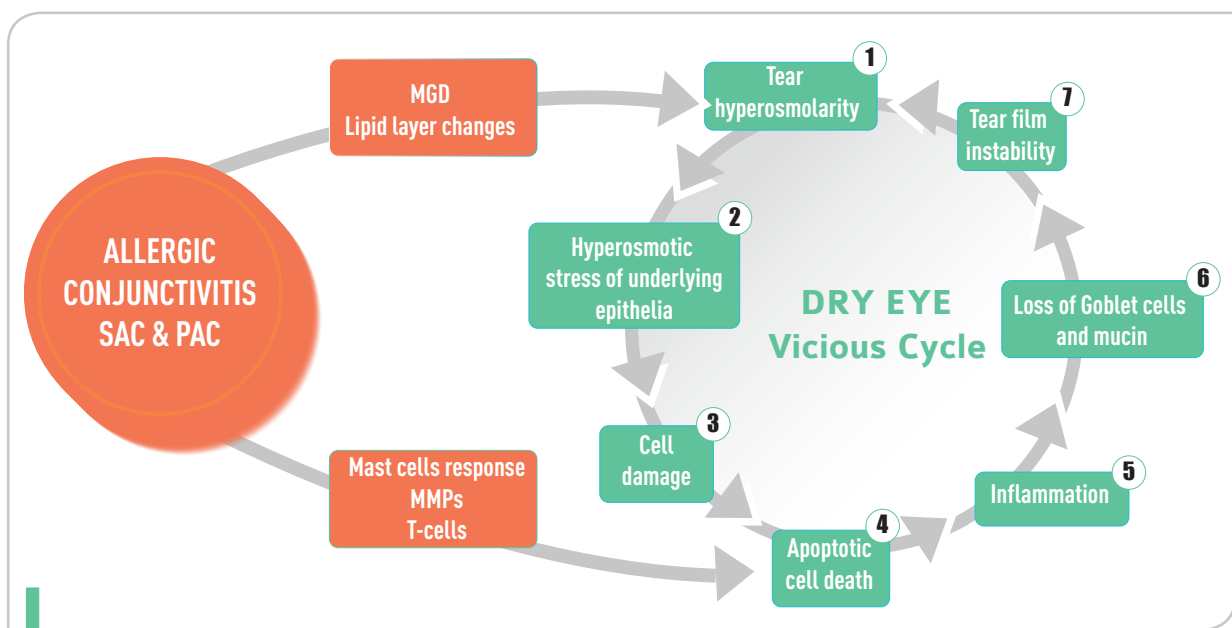


Fig. 1.3. The allergy mediated entry points to the DED vicious cycle

Dry eye disease interlinks with allergic reaction

When it comes to symptoms, DED and ocular allergy can be quite similar, making the differential diagnosis challenging. Common manifestations include redness, burning, erythema, but tearing with itching is a hallmark of allergic reaction, and foreign body sensation is a hallmark of DED. As mentioned before, ocular allergy predisposes to dry eye, making the clinical manifestations more obscure. Patients with ocular allergies have reduced BUT⁽²²⁾, indicating that allergic conjunctivitis potentiates the vicious cycle of dry eye.

The relationship between the two conditions stems from inflammation which is a common feature and sets the background for the disease progression. Chronic inflammation leads to composition changes of the tear film by reducing the number of goblet cells and the amount of mucin produced. This results in tear film instability, increased evaporation etc. Thus, the inflammation associated with the allergic reaction generates a favorable environment for the development of dry eye.

ALLERGIC CONJUNCTIVITIS AND DRY EYE DISEASE IN CHILDREN

Ocular surface health in children may be adversely affected by similar ocular, systemic and environmental factors as in adults. However, clinical and epidemiological factors for paediatric ocular surface disease in general and allergic conjunctivitis as well as dry eye disease have been less investigated compared to the adult population.

SAC and PAC are the two most common forms of ocular allergy in children, but they are still less frequent than in young adults. In general, 80% of patients are younger than 30 years old.

- VKC is predominantly a male paediatric disease, usually subsiding after puberty, whereas
- AKC is not very common. The clinical presentation of the allergic conditions in childhood could be milder, but they share common features and pathophysiology

Paediatric dry eye is considered as a rare condition, mainly associated with congenital, autoimmune and inflammatory disorders. However, it is not as well investigated as in adults, so its diagnosis is often overlooked⁽³⁾.

On the other hand, exposure to commonly identified environmental factors especially the use of electronic visual digital devices or extended screen viewing via smartphones, tablets and/or computers and myopia management techniques such as contact lens wear or use of daily preserved eye drops are factors that play an increasingly deleterious role among the paediatric population.

The principal treatment goal of AC in children is:

- to control its symptoms
- to improve the QoL of patients which involves minimizing, or at least reducing, itching, redness, tearing, and edema of the conjunctiva and eyelids.

Introduction to pharmacological agents is necessary when allergen avoidance and lifestyle modifications, including avoidance of outdoor activities, reducing screen time etc, do not provide adequate symptom relief.

The primary goal for AC management in children should be to prevent or alleviate the symptoms as rapidly as possible with the fewest number of pharmacologic agents and the regimen that is least disruptive to the children's lifestyle and everyday activities.

The different classes of drugs indicated in the treatment of AC in pediatric patients include:

- topical decongestants (for children of 2 years and older)
- systemic antihistamines,
- topical antihistamines (not approved for infants less than 2 years old)
- mast cell stabilizers
- combined antihistamine and decongestants
- combined antihistamine and mast cell stabilizers
- nonsteroidal anti-inflammatory drugs, and corticosteroids⁽²³⁾.



KEY MESSAGES

Most common types of ocular allergies are the Seasonal Allergic Conjunctivitis (SAC) & Perennial Allergic Conjunctivitis (PAC). The symptoms when accompanied by allergic rhinitis can severely affect patient's quality quality of life.

Ocular toxicity from preservatives such as BAK, can lead to drug related allergy.

The primary goal for AC management in children should be to prevent or alleviate the symptoms as rapidly as possible with the minimum number of pharmacologic agents and the regimen that is least disruptive to children's lifestyle and everyday activities.

Different forms of severe allergy have to be considered very carefully to limit the risk of complications.

An obvious link exists between Dry Eye and Allergy that needs to be clearly understood to treat patients according to the symptoms and physiopathology.



2

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS OF DED & ALLERGY

2.1 HISTORY-TAKING

Ocular allergy and DED are common, relevant, symptomatic, non mutually exclusive conditions affecting the ocular surface. Since they share common clinical and biochemical features, a meticulous history-taking is important to differentiate them and reach an accurate diagnosis.

Allergy Evaluation⁽¹⁾

The eye is a target organ for allergy because it is the first line of contact with airborne allergens. 97% of allergic conjunctivitis cases are associated with rhinitis, 56% with asthma, and 30% with eczema⁽¹⁾.

- Ocular allergies are always associated with characteristic symptoms like ocular itching, swelling, and tearing, resulting from mast cell degranulation and histamine release⁽¹⁾.
- Eye pruritus is highly indicative of allergy, but it can misdirect the diagnosis. The location of the pruritus must also be specified:
 - » if conjunctival, it is indicative of conjunctivitis,
 - » if on the eyelid margin it will more likely reveal demodex infestation or seborrhoeic blepharitis, whereas if it is cutaneous it is indicative of eczema⁽²³⁾.
- Eyelid swelling on waking and the presence of morning aqueous discharge are also indicative of allergy.
- The efficacy of allergy medication, particularly antihistamines, is also a very strong factor suggestive of an eye allergy. Allergic conjunctivitis that does not respond to an antihistamine treatment is generally a mixed condition, where allergy is just one of the components.
- 10 to 20% of ocular allergic patients have negative systemic allergy tests.
- A family history of atopy is also a significant factor, since the risk is multiplied by 4 if one parent is atopic and multiplied by 10 if both parents are atopic.
- Environmental triggers such as cosmetics, pets, seasonal pollen or domestic mites and dust can support the diagnosis.

DED - OSD Evaluation

The characteristic manifestations of dry eye disease consist of:

- Foreign body sensation, sandy or burning sensation and gritty feeling during blinking (indicative but non-specific)⁽¹⁵⁾.

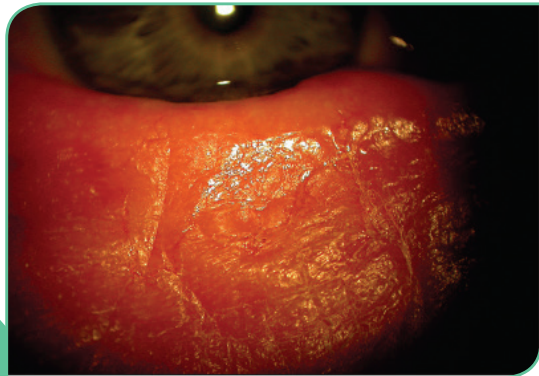
- Inability to open the eyes in the morning because of drying during sleep (relatively specific).
- Visual disturbance, such as intermittent blurry vision clearing with eye rubbing and functional disturbance in daily activities such as computer, book reading and driving may be present.
- Dryness of the mouth, skin or vagina is a fundamental symptom of DED suggesting systemic involvement, as in Sjögren syndrome.
- Presence of an autoimmune disorder such as Rheumatoid Arthritis, thyroid ophthalmopathy and other immune mediated diseases are suggestive of secondary Sjögren syndrome.
- Facial skin disorders such as acne, rosacea or seborrheic dermatitis may suggest Meibomian gland dysfunction (MGD) and blepharitis.
- Hormone disorders or replacement treatment in menopause and certain medications like beta blockers, anticholinergic drugs, antidepressants or retinoids may elicit DED⁽²⁴⁾.

2

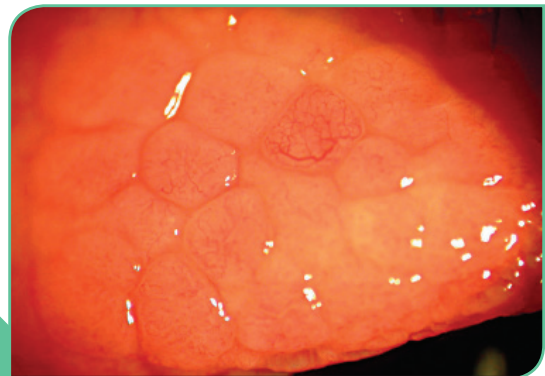
.2 CLINICAL EXAMINATION

Signs of allergy

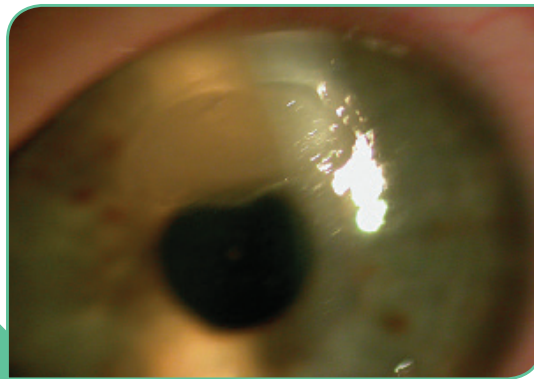
- Eyelid eczema, contact dermatitis and allergy related blepharitis are characteristic changes on the eyelid skin⁽²⁵⁾.
- Giant papillary conjunctivitis on the upper palpebral conjunctiva is characteristic of allergic response.
- Limbal nodules or Trantas' dots.
- A vernal plaque or ulcer.



Pict. 2.1. Eyelid eczema.
Picture courtesy of Dr. Doan



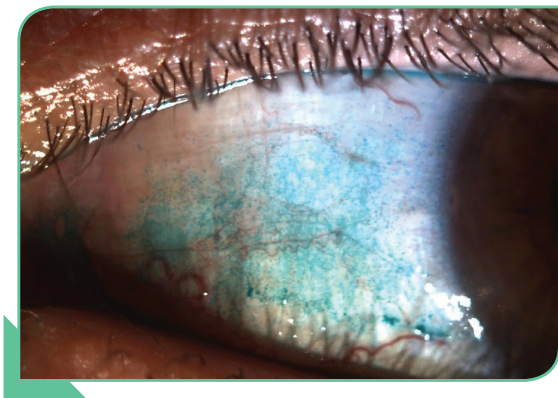
Pict. 2.2. Giant papillae in vernal keratoconjunctivitis.
Picture courtesy of Dr. Doan



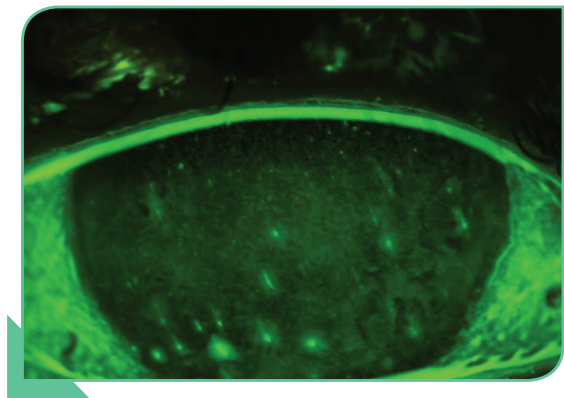
Pict. 2.3. Vernal plaque in vernal keratoconjunctivitis.
Picture courtesy of Dr. Doan

Signs of DED

- Dry or filamentous keratoconjunctivitis, with superficial punctate keratopathy, lissamine green staining on the conjunctiva and lid margin changes, are specific and signal severe dryness (Pict. 2. 4)⁽²⁴⁾.
- A Schirmer's test with a measurement less than 10 mm in 5 minutes, with no anaesthesia, is specific for aqueous deficient DED⁽¹⁰⁾.
- Rosacea (telangiectasias, flushes, hyperemia, papulopustular facial rashes, rhinophyma) or facial seborrheic dermatitis (irritation and redness with oily flakes between the eyebrows, sides of the nose and scalp) and acne in puberty should prompt testing for blepharitis.



Pict. 2.4. Lissamine green staining of the bulbar conjunctiva indicating goblet cell damage on moderate DED with lack of corneal or eyelid involvement. Picture Courtesy of Prof. Boboridis.



Pict. 2.5. Intense punctate fluorescein staining of the cornea with visible filaments on keratopathy from severe DED. Picture Courtesy of Prof. Boboridis.

The non-specific signs that could be associated with allergy or dryness

Palpebral conjunctivitis is a generic tissue response found both in ocular allergy but also in cases of DED with inflammation⁽⁷⁾.

Mucinous discharge occurs in allergy, but also in DED.

Blepharitis can be associated with rosacea and seborrheic dermatitis, but also with severe dry conjunctivitis or an allergic blepharitis.

A tear break-up time (BUT) of less than 10 seconds demonstrates tear instability with lipid deficiency from several possible causative factors.

2.3 OVERVIEW OF CAUSATIVE FACTORS

The following mapping-table presents the various etiopathologies of allergy and dry eye disease. The treatment of allergy and dry eye disease is complex as a multitude of underlying mechanisms may be responsible for a variety of symptoms, whereas on the other hand, the diagnostic criteria are characterized by low reliability.

Some of the key factors contributing to the gradual pathology of allergy and dry eye include tear hyperevaporation and hyposecretion, tear film instability, mucus layer abnormalities and allergy. These conditions often overlap making exact diagnosis and treatment quite challenging.

The illustration (Fig. 2.1) presents the different pathologies along with classifications, underlying or concomitant conditions and may assist the practitioner to arrive to a safer evaluation of each case.

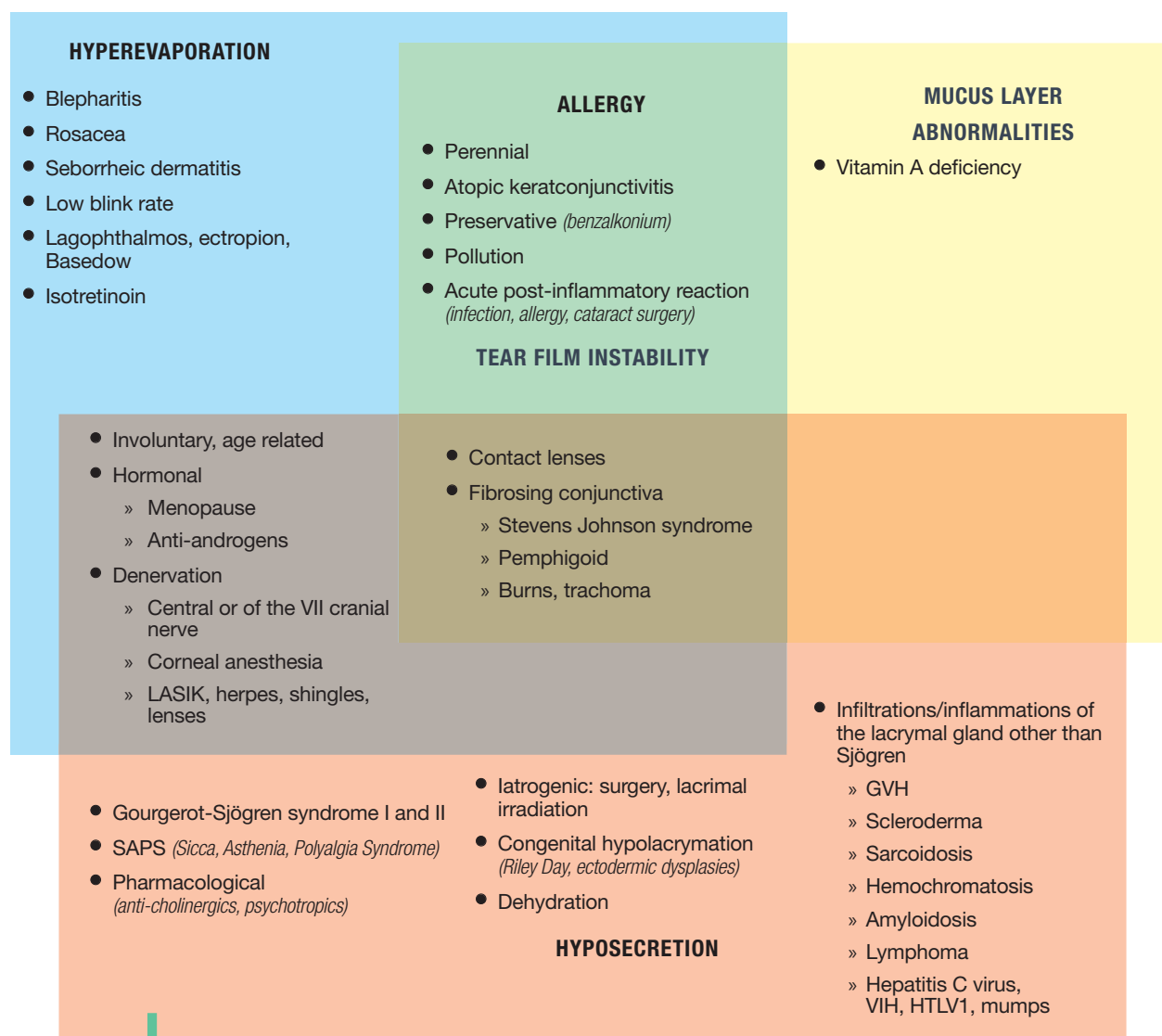


Fig. 2.1. Causative factors of dry ey disease, adapted from Dr. Doan⁽²⁷⁾.

The most common triggers of an allergic response can be divided in two main categories: airborne allergens and contact allergens. Airborn allergens also tend to be seasonal such as pollen whereas contact allergens can be found in a variety of sources spanning from personal care products to industrial chemical and pharmaceuticals. The following figure (Fig. 2.2) presents the most common airborne and contact allergens.

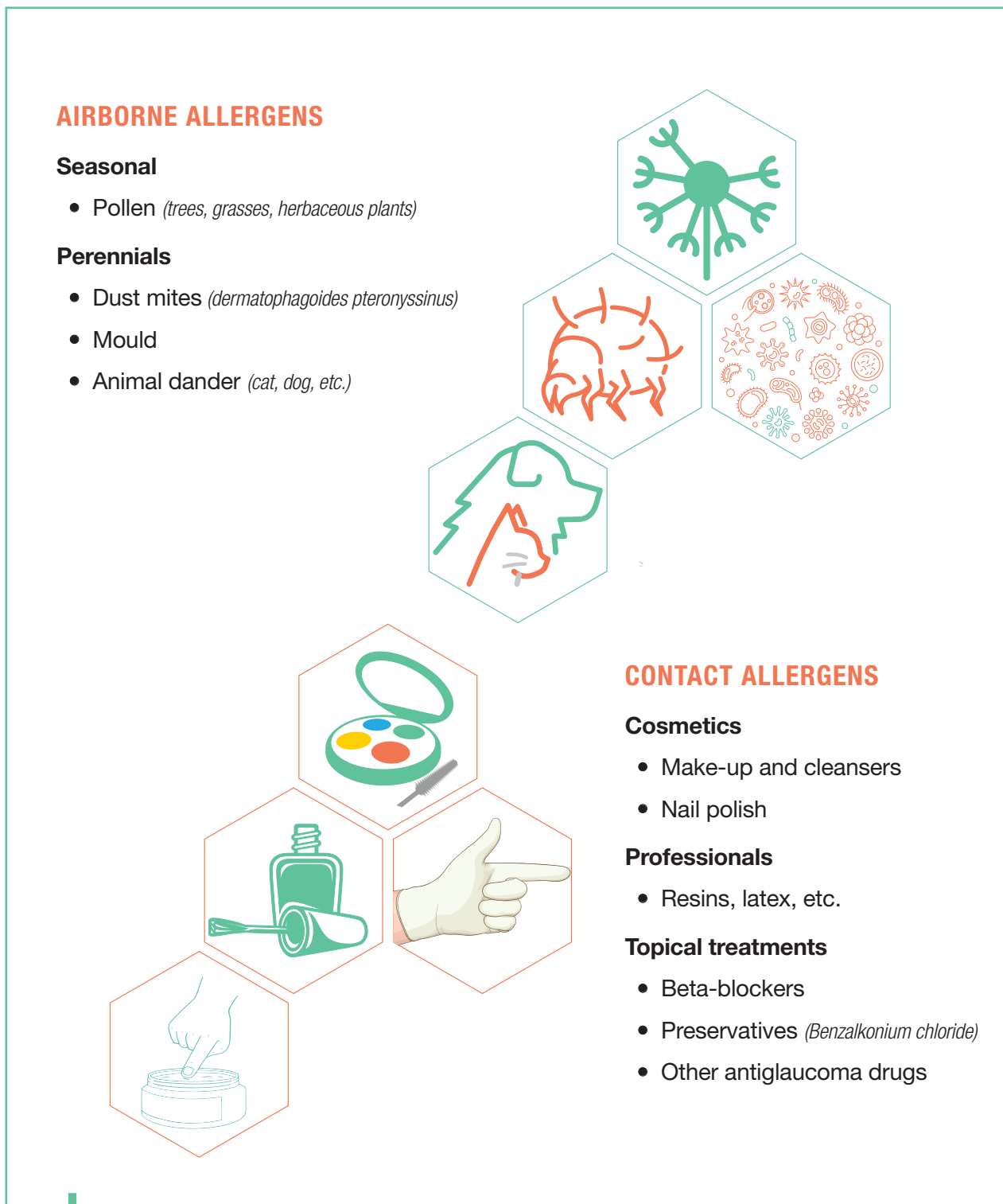


Fig. 2.2. Main categories of allergens

Medical / Allergist assessment

This first and foremost requires tests for Sjögren syndrome (SGS):

- Antinuclear factors: anti-SSA and SSB antibodies which are specific to SGS⁽²⁸⁾.
- Markers of other auto-immune diseases are also tested within a context of secondary SGS:
- Anti-native DNA antibodies (lupus)
- Rheumatoid factors, anti-citrulline antibody (rheumatoid polyarthritis)
- Thyroid test (Hashimoto thyroiditis)
- A biopsy of the accessory salivary glands brings certainty to the diagnosis when there is a mononuclear infiltrate and grade 3 or 4 glandular fibrosis according to the Chisholm-Mason classification.
- The internist's, rheumatologist's, dermatologist's or endocrinologist's point of view is often useful.

Ophthalmologist assessment

Depending on the context and for a differential diagnosis, the presence of *Demodex* on the lashes and *Chlamydia Trachomatis* by conjunctival scraping can also be investigated⁽⁷⁾.

In daily practice, for a positive allergy and dryness diagnosis, the investigations carried out are: the conjunctival provocation test (after an allergy assessment), tear IgE for the allergy, and the internist's assessment for dryness.

Local eye assessment may incorporate the following steps as it is shown at Fig. 2.3.

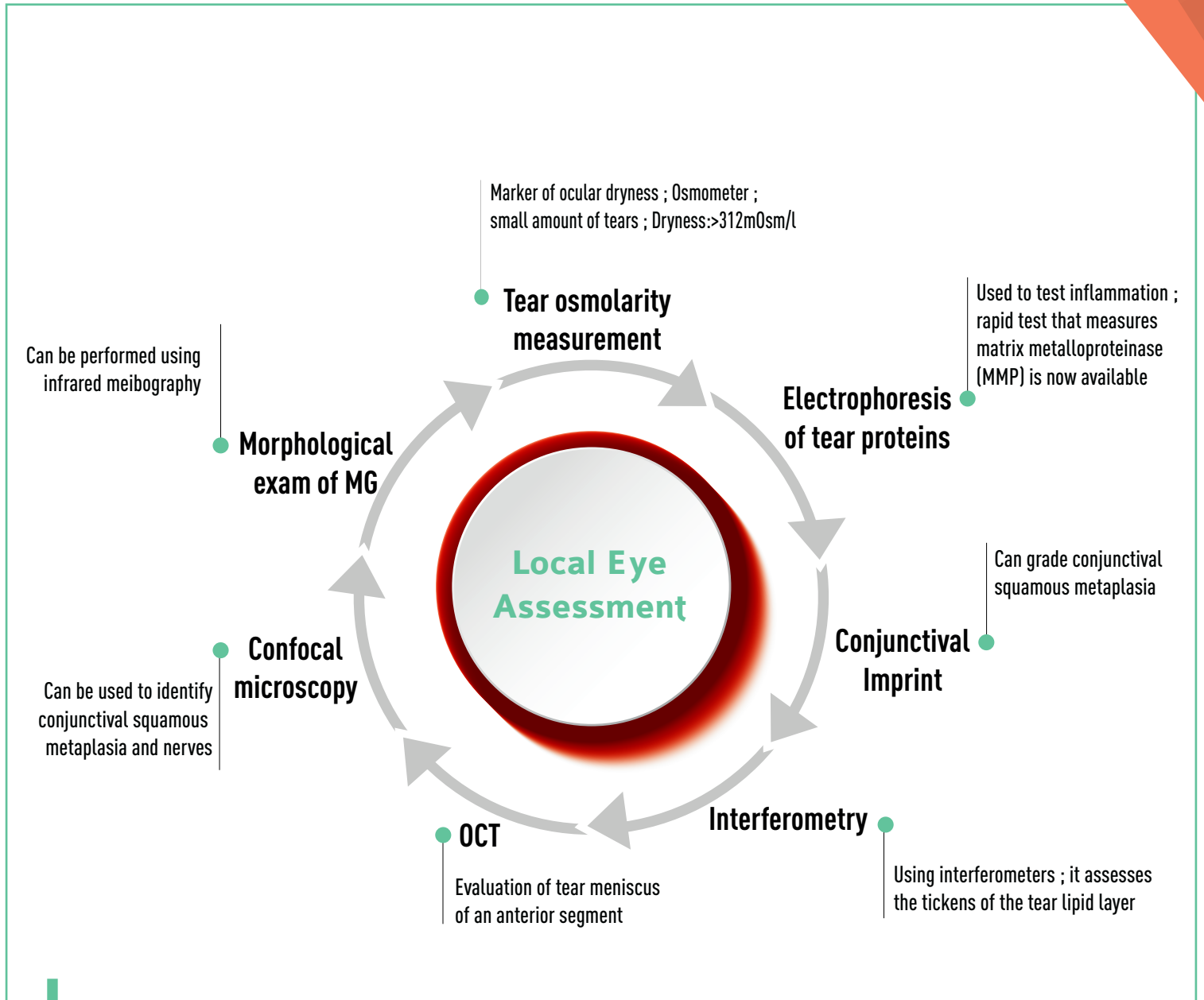


Fig. 2.3. Steps of local eye assessment⁽⁷⁾



KEY MESSAGES

Carefully examination will assist differential diagnosis :

Specific signs of allergic conjunctivitis

- Eyelid eczema & allergy related blepharitis
- Giant papillary conjunctivitis
- Trantas' dots
- Vernal plaque

History taking is important to differentiate the two diseases and reach an accurate diagnosis.

Causative factors could be strongly interlinked. Airborne or contact allergens can be easily identified by questioning your patient.



3

STRATEGY FOR OCULAR ALLERGY MANAGEMENT

3.1 GENERAL CONSIDERATION OF OCULAR ALLERGY AND DED MANAGEMENT

Ocular allergy and dry eye disease diagnosis and management can be challenging at times mainly due to the complex interactions between the different components involved, and the wide range of conditions that can result in similar functional effects on the ocular surface. Both however are quite common with increasing prevalence among both adult and youth populations and hence pose a growing healthcare problem, that affects all ages⁽³⁾.

An effective approach to the general macro-management of ocular allergies leading to ocular surface disease such as dry eye, must aim primarily to eliminate exacerbating factors and lifestyle habits, address the ocular allergy and tear film instability by supporting the tear film and protecting the ocular epithelium, normalize tear film hyperosmolarity, reduce ocular inflammation, normalize the meibomian gland dysfunction and reverse the ocular surface damage⁽³⁾ (Figure 3.1).

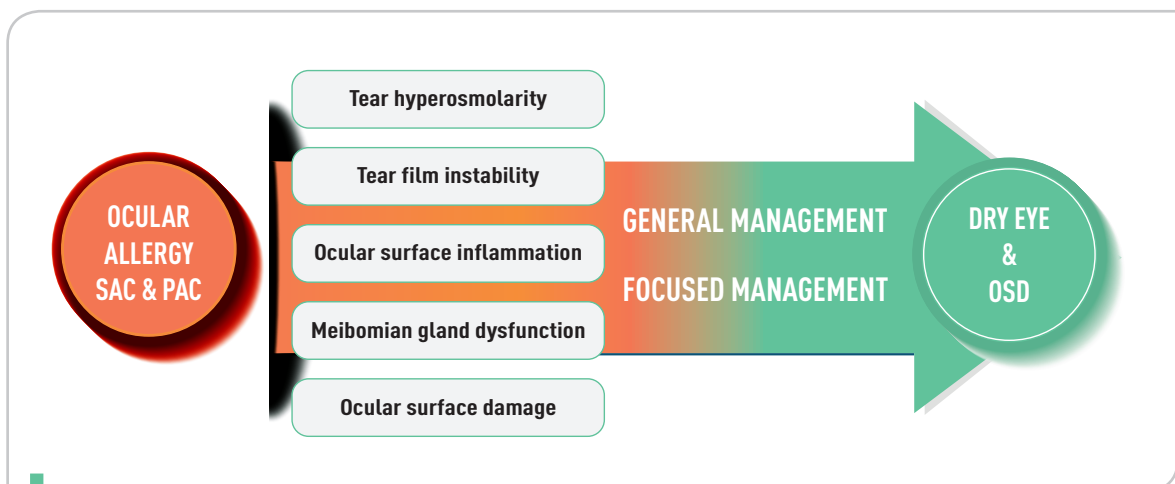


Figure 3.1: The management of these conditions in order to alleviate the effect of ocular allergy on dryness includes general, environmental and lifestyle modifications, symptom relief products such as trehalose and hyaluronic acid containing artificial tears and focused pharmacological management to address more severe conditions.

.2 GENERAL MANAGEMENT: PRIMARY MEASURES, LIFESTYLE INTERVENTIONS AND ELIMINATION OF EXACERBATING FACTORS

Patients suffering from seasonal or perennial allergic conjunctivitis (SAC or PAC) and mild dry eye symptoms can be affected by several environmental and lifestyle exacerbating factors. In terms of SAC and PAC, special care must be given to avoid contact with allergenic precursors such as pollen, dust mites, animal dander, mould spores and local irritants (Figure 3.2). The conventional lifestyle modifications for the management of dryness in allergy are focused on avoiding factors that may exacerbate dry eye symptomatology, including avoiding low humidity environments and exposure to air drafts, high indoor temperatures, prolonged screen use, contact lens wear, avoiding the use of cosmetics, as well as certain medications and agents that have been linked to dry eye development, such as corticosteroids and systemic anti-histamines, and topical ocular medications containing preservatives such as BAK⁽²⁹⁾.

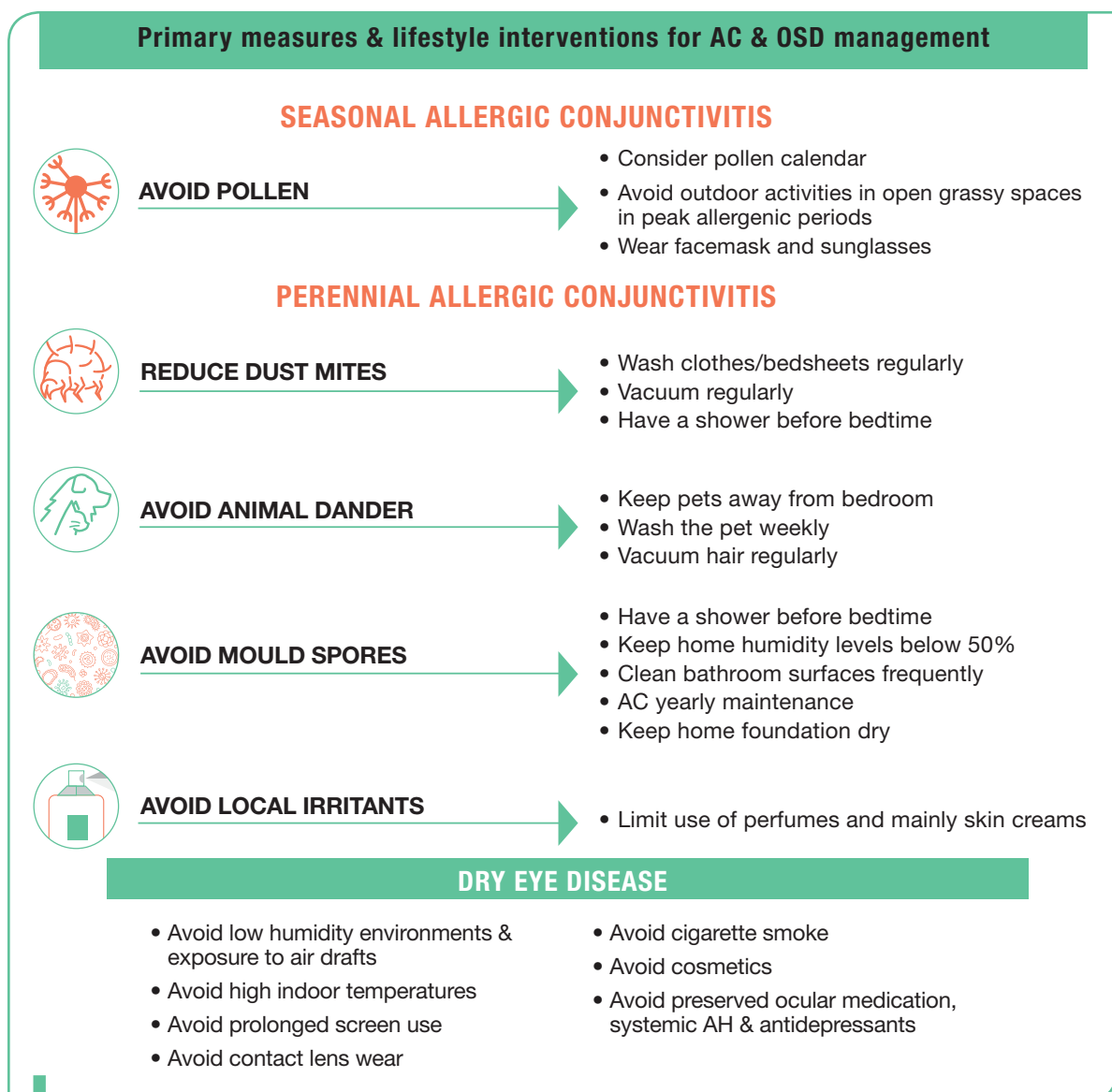


Figure 3.2: Primary measures and lifestyle interventions for Allergic Conjunctivitis and related dry eye management.

There is currently a wide range of solutions that provide symptom relief via ocular lubrication, and a variety of agents that support the tear film, protect the epithelium and reduce inflammation. Techniques such as punctal occlusion in order to achieve tear retention and treating concomitant eyelid disorders such as MGD may also be considered (Fig. 3.3). A significant progress in ocular disease management has also been the elimination of preservatives, such as benzalkonium chloride (BAK) and polyquad, from topical ophthalmic pharmacological solutions and ocular lubricants.

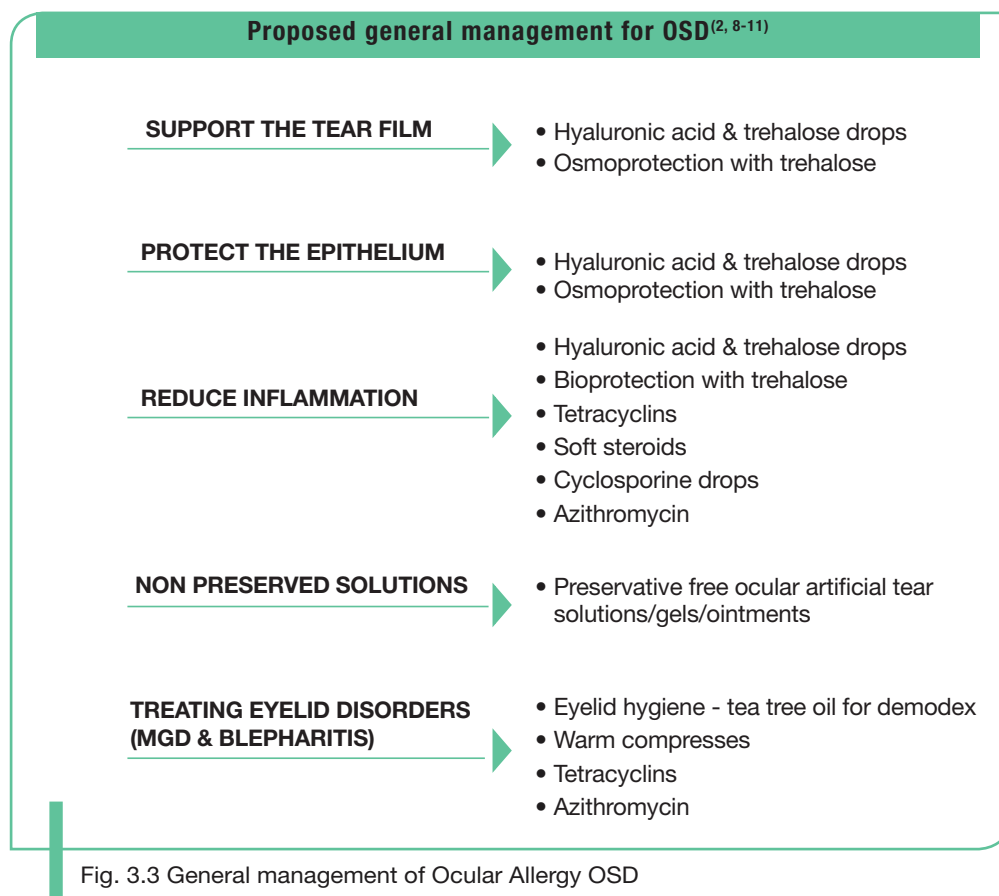


Fig. 3.3 General management of Ocular Allergy OSD

Osmoprotectant substances, such as erythritol, L-carnitine and glycerol have successfully been utilized in fixed combination tear substitutes along with hyaluronic acid (HA)^(30, 31).

HA is used in multiple types of artificial tears due to its viscoelastic and hydrating properties. Another important characteristic is its mucoadhesiveness through which it can function as an effective coating, providing long lasting protection for the ocular surface and epithelium. High molecular weight HA has a reparative effect on the ocular surface, stimulating epithelial migration, and inhibiting the expression of pro-inflammatory mediators such as IL-6 and IL-8 and as such it can work also against inflammatory conditions^(31, 32).

Trehalose is a naturally occurring disaccharide with a bioprotective role that ranges from offering osmoprotection to maintaining the integrity of cellular components and reducing cell death⁽³³⁾. The addition of trehalose in hyaluronic acid ocular solutions for moderate and severe allergy originated dryness has been linked to observed increased tear film thickness, underlined by a significant improvement of conjunctival epithelium metaplasia as well as a dramatic reduction of cytokines linked to inflammation⁽³⁴⁾. Several studies to date have demonstrated that HA-trehalose solutions provide profound symptomatic relief and better patient satisfaction for OSD patients compared to HA solution alone, based on ocular surface disease index (OSDI) assessments⁽³⁵⁾ and dry eye questionnaires⁽³³⁾. Eye drop and eye gel formulations of HA-trehalose ocular treatments have also been compared in patients with moderate to severe DED, and both demonstrated similar improvements of DED signs and symptoms with corneal fluorescein and conjunctival lissamine green staining scores decreased and tear break up times increased in both groups⁽³⁶⁾. Additionally, HA-trehalose has a better safety profile regarding ocular side effects compared to HA alone⁽³³⁾.

The toxicity of BAK and other preservatives has been well established, causing tear film instability, ocular surface changes, conjunctival inflammation, epithelial apoptosis and subconjunctival fibrosis⁽³⁷⁾. Multiple studies have demonstrated an improved profile on ocular toxicity in preservative free ophthalmic solutions for the treatment of allergic conjunctivitis and other ocular diseases^(7, 8, 24).

Preservative-free formulations are of primary importance in severe dry eye cases with ocular surface disease and lacrimal gland secretion impairment, greatly reduced tear secretion, punctal occlusion and for patients on multiple preserved medications for chronic eye disease. Additionally, preservative free formulations are necessary in case of an identified preservative allergy or epithelial toxicity due to preservatives⁽³⁸⁾.

As a result, the pharmaceutical industry has recently been oriented towards single dose vials or multidose devices fitted with filters, preventing microbial contamination of a preservative free ophthalmic solution (e.g. the ABAK® system)⁽³⁹⁾.

In this context preservative-free products should be preferentially prescribed⁽⁴³⁾.

A KEY ROLE FOR PRESERVATIVE-FREE PRODUCTS^(38,39)

- Patients with severe dry eye with ocular surface disease and lacrimal gland secretion impairment
- Severe DES patients with greatly reduced tear secretion
- Severe DES patients with punctal occlusion
- Patients on multiple preserved medications for chronic eye disease
- Preservative allergy
- Epithelial toxicity from preservatives

3

3.4 FOCUSED MANAGEMENT OF OCULAR ALLERGY

Topical ophthalmic treatments include antihistamines, mast cell stabilizers, multi action agents with antihistaminic and mast cell stabilizing properties, NSAIDs, topical steroids, and immunotherapies. Systemic treatment includes treatment with oral antihistamines. The different treatments should be prescribed under careful consideration of the severity of the patient's condition and tailored to individual patient characteristics, such as age and underlying comorbidities, diagnosis, with mild and moderate SAC & PAC generally to be treated with antihistamines, mast cell stabilizers, multi action agents (Figure 3.4) leaving NSAIDs, steroid treatments and immunotherapies for more severe and persistent cases (Figure 3.5).

Management of mild to moderate Seasonal & Perennial Allergic Conjunctivitis

Antihistamines (AH)

Antihistamines prevent inflammatory events triggered by histamine and alleviate signs and symptoms of SAC and PAC, particularly itching^(40, 41). Topical second generation antihistamines such as emedastine and levocabastine, have a favorable safety profile compared to first generation antihistamines and applied 4 times daily have a proven efficacy compared to placebo as reported by several clinical trials⁽⁴⁰⁻⁴²⁾. Systemic treatment with oral antihistamines such as cetirizine and loratadine can be included as an additional measure but it has been associated with severe adverse effects, thus is only indicated with coexisting rhinitis^(29, 41).

Mast Cell Stabilisers (MCS)

Mast cell stabilisers including Sodium cromoglicate, nedocromil sodium, lodoxamide and pemirolast potassium are used in common clinical practice to reduce redness, hyperemia, itching and irritation by preventing the release of inflammatory mediators as a result of blocking the degranulation of mast cells. Multiple daily instillations (2-6 times) are required to maintain symptom relief^(40, 41, 43).

Multi Action Drugs

Multi-action antihistamine-mast cell stabilisers (AH-MCS) are the first line agents for the treatment of allergic conjunctivitis because they combine mast cell stabilizing and antihistaminic properties and demonstrate both prophylactic and therapeutic efficacy.

Some successful multi-action AH-MCS include **ketotifen**, olopatadine, epinastine, azelastine, bepotastine, and alcaftadine⁽⁴⁰⁾. Multi-action AH-MCS provide relief of redness, hyperemia, itching and

irritation associated with SAC with only mild side effects including mild burning during instillation and cold like symptoms^(40, 41, 43). Their efficacy and safety profile has been extensively studied and compared to other ocular SAC/PAC treatments based on a systematic review and/or meta-analysis of numerous clinical trials⁽⁴²⁾.

The use of multi-action AH-MCS is simplifying the regimen for treatment of SAC & PAC as only 1-2 daily instillations are required to maintain symptom relief, which positively affects patient compliance and leads to lifestyle improvement^(7, 43, 45).

SPECIFIC ROLE OF KETOTIFEN

- A recent study, comparing preservative free ketotifen and preserved-olopatadine demonstrated similar efficacy but better ocular tolerance to the preservative-free ketotifen treatment⁽⁴⁴⁾.
- Different formulations of ketotifen have also been compared, and unpreserved ketotifen 0.025% was found more effective and better tolerated than ketotifen 0.05%, for the treatment of SAC⁽⁴⁵⁾.
- Unpreserved ketotifen 0.025% has been shown to be less toxic formulation compared to the other available topical treatments for SAC, with good control of symptoms and signs. It is considered the optimum solution combining efficacy and tolerability for the management of ocular allergy⁽⁷⁾.

An interesting anti-degranulating agent with mast cell stabilizing properties as well as additional anti-eosinophilic properties is the compound N-acetyl-aspartyl-glutamate (NAAGA). The antiallergic compound NAAGA directly inhibits leukocyte adhesion to endothelial cells induced by pro-inflammatory stimuli, and abrogates TNFalpha-induced expression of adhesion molecules on granulocytes and endothelial cells⁽⁴⁶⁾. This capacity to block overexpression of selectins and integrins induced by pro-inflammatory stimuli also makes NAAGA a potent anti-inflammatory agent. In cases, NAAGA has been shown to be more effective than levocabastine in controlling the symptoms of conjunctival inflammation and with improved tolerability⁽⁴⁷⁾. NAAGA has demonstrated efficacy in alleviating dry eye syndrome symptoms, coupled with an additional anti-inflammatory effect, based on leukotriene inhibition, when used in a preservative-free formulation⁽⁴⁸⁾.

N-ACETYL-ASPARTYL-GLUTAMATE (NAAGA)

- NAAGA is a multi-action agent
- Acts as a mast cell stabilizer
- Blocks complement activation
- Inhibits synthesis of leukotrienes
- Has anti-inflammatory and anti-eosinophilic properties

MANAGEMENT OF MILD- MODERATE SAC & PAC

ANTIHISTAMINES (AH)

- Topical: emedastine, levocabastine
- Systemic: cetirizine, loratadine



MECHANISM OF ACTION

Competitive agonists of H1 receptors
↓ histamine triggered inflammatory events

FACTS

- Topical 2nd generation AH more favourable safety profile than 1st
- Exacerbation of ocular adverse effects due to antihistamine's anticholinergic effect leading to reduced lacrimation is a concern
- Systemic AH only indicated with coexisting rhinitis

MAST CELL STABILISERS (MCS)

- Sodium cromoglycate, nedocromil sodium, lodoxamide, pemirolast potassium



MECHANISM OF ACTION

Block mast cell degranulation leading to prevention of inflammatory mediators release

FACTS

- The use of MCS should be mainly prophylactic

DUAL ACTION AGENTS

- AH-MCS: ketotifen, epinastine, bepotastine, azelastine, alcaftadine, olopatadine
- NAAGA



MECHANISM OF ACTION

Combined antihistamine or anti-inflammatory, and mast cell stabilizer mechanisms of action

FACTS

- 1st line agents of SAC & PAC treatment due to combined prophylactic and therapeutic properties
- Unpreserved **ketotifen** better ocular tolerance than unpreserved olopatadine⁽⁴⁴⁾
- Ketotifen 0.025% more effective and better tolerated than 0.05%⁽⁴⁵⁾
- **NAAGA** is a dual action agent that is more effective than levocabastine, with an added anti-inflammatory effect⁽⁴⁸⁾

Figure 3.4. Pharmacological management of mild to moderate ocular allergies

Management of moderate to severe Seasonal and Perennial Allergic Conjunctivitis

NSAIDs & Corticosteroids

Many of the ocular surface diseases are associated or lead to an inflammatory state. In more severe and unresponsive cases to anti-allergic medications described above, anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may be prescribed.

Ketorolac is the only NSAID approved for the topical treatment of seasonal allergic conjunctivitis. NSAIDs interfere with mediators of the late-phase response, and block prostaglandin production. Because of the availability of other classes of agents with established efficacy and proven tolerability profiles, ophthalmic ketorolac is recommended for only occasional use in the treatment of acute allergic conjunctivitis not responsive to other agents. In addition, this class of topical medications is known for superficial corneal adverse events, therefore they are not routinely used in allergic OSD⁽⁴⁹⁾.

The first choice of treatment for ocular inflammation is topical steroids and the selection of the proper agent depends on the severity of inflammation. Corticosteroids exert their wide anti-inflammatory action via suppressing the activation, recruitment and production of inflammatory mediators, increasing histaminase production, preventing mast cell degranulation thus preventing histamine production and inhibiting the activity of inflammatory cells. Corticosteroids have been shown to have remarkable anti-inflammatory properties and lead to reduction of most ocular signs and symptoms of SAC. In mild and moderate ocular surface inflammation, mild topical steroids like fluorometholone, loteprednol or hydrocortisone can be used on an 'as required' basis or as short tapering courses with loteprednol showing minimal risk for transient intraocular pressure rise^(41, 51, 54). The longest lasting effect is exhibited by hydrocortisone, lasting up to 7 days compared to a 24 hours lasting effect of the rest⁽⁵⁴⁾. Any treatment with either mild steroids or more potent corticosteroids, such as dexamethasone should be of short duration and the patient should be closely monitored due to the associated severe ocular side effects such as increased Intraocular Pressure (IOP) and induction of glaucoma and cataract^(40, 41, 50).

A frequent dosage of 4 times daily or more is required for both NSAID and steroids⁽⁴³⁾.

Immunomodulation

In severe and persistent cases of ocular allergic reaction, initiation of topical immunotherapy may be necessary and is specifically indicated for patients with severe adverse effects from corticosteroids⁽⁴²⁾. Immunomodulators such as cyclosporine, which exerts its effect by inhibiting antigen dependent T-cell stimulation, although most frequently used for treatment of VKC, it has a proven efficacy in SAC & PAC management and improves symptoms of itchiness and eye redness with excellent safety profile and tolerability^(24, 43, 52, 53).

MANAGEMENT OF MODERATE TO SEVERE SAC & PAC

NSAIDS

- Ketorolac



Daily Instillations

MECHANISM OF ACTION

Block the cyclooxygenase pathway and prostaglandin production

FACTS

- Should be prescribed to severe and unresponsive cases to first line medications

CORTICOSTEROIDS

- Dexamethasone, loteprednol



Daily Instillations

MECHANISM OF ACTION

↓inflammatory mediators, ↑histaminase production, ⊖mast cell histamine production, ⊖inflammatory cell activity

FACTS

- Severe and unresponsive cases to first line medications
- Treatment should be of short duration
- Patient should be closely monitored

IMMUNOTHERAPIES

- Cyclosporine



Daily Instillations

MECHANISM OF ACTION

Inhibits antigen dependent T-cell stimulation

FACTS

- Allergist input necessary
- Recommended for patients experiencing severe side effects to corticosteroids

Figure 3.5. Pharmacological management of moderate to severe ocular allergies

KEY MESSAGES

Management options should stabilize the tear film, protect the ocular surface epithelium and address the resulting inflammation from mast cell degranulation and histamine release.

Unpreserved Ketotifen 0,025% is less toxic formulation compared to the other available topical treatments, with good control of symptoms and signs, representing the optimum choice for efficacy and tolerability on the management of ocular allergy.

Multi drug actions are very useful in anti-allergic therapeutic strategy as well as trehalose eye drops in Dry Eye Disease.

BAK and other preservatives have been shown to induce local toxicity and then favour inflammation.

Preservative-free formulations should be preferred.

IN A FEW WORDS...

Management options should stabilize the tear film, protect the ocular surface epithelium and address the resulting inflammation from mast cell degranulation and histamine release.

Unpreserved Ketotifen 0,025% is the least toxic formulation compared to the other available topical treatments, with good control of symptoms and signs, representing the optimum choice for efficacy and tolerability on the management of ocular allergy.

Osmoprotective substances defend the desiccated epithelium and especially trehalose is proven to offer both bio-protection and cellular anti-inflammatory action.

Preservative-free formulations are necessary for the management of Ocular Allergy & DED and should be preferentially prescribed.



CONCLUSIONS

Ocular surface disease and tear film instability are closely related to ocular allergy sharing interlinked pathophysiology and clinical presentations. Dry eye disease is often a precursor or comorbidity to allergic conjunctivitis. Careful and systematic evaluation of symptoms and signs, mainly of ocular itching which is the quintessential symptom of allergic reaction can lead to the correct diagnosis and avoid the commonest clinical pitfall is over-diagnosing allergic conjunctivitis on the ground of simple dry eye disease. Other conditions which present with diagnostic challenges are meibomian gland dysfunction with demodex infestations presenting with persistent itching and the toxic effect of preservatives, mainly benzalkonium chloride (BAK), on the ocular surface from prolonged topical treatment which may involve an initial allergic reaction and ocular itching.

Management options should stabilize the tear film, protect the ocular surface epithelium and address the resultant inflammation from mast cell degranulation and histamine release. It is of paramount importance to emphasize that only unpreserved medications should be chosen in dry eye and allergy cases as preservatives induce additional toxicity and inflammation. A stepped approach should include artificial tears containing hyaluronic acid which have been proven the most efficient option for the tear film support. Osmoprotective agents defend the desiccated epithelium and Trehalose is proven to offer both bioprotection and cellular anti-inflammatory action. Unpreserved Ketotifen 0,025% is the least toxic formulation compared to the other available topical treatments, with good control of symptoms and signs, representing the optimum option for efficacy and tolerability on the management of ocular allergy. In persistent cases the introduction of mild, surface acting topical steroids is necessary and Hydrocortisone offers good control of inflammation with minimal side effects even in prolonged treatment. In more severe cases, topical or systemic immunomodulation with T-cell control is necessary possibly in collaborations with an allergist.

REFERENCES

1. Leonardi, A., et al., Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy*, 2012. 67(11): p. 1327-37.
2. Patel, D.S., et al., Allergic eye disease. *BMJ*, 2017. 359: p. j4706.
3. Villani, E., G. Rabbio, and P. Nucci, Ocular allergy as a risk factor for dry eye in adults and children. *Curr Opin Allergy Clin Immunol*, 2018. 18(5): p. 398-403.
4. Leonardi, A., et al., Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol*, 2015. 15(5): p. 482-8.
5. Doan, S., et al., (Efficacy of topical 2% cyclosporine A as a steroid-sparing agent in steroid-dependent vernal keratoconjunctivitis). *J Fr Ophtalmol*, 2007. 30(7): p. 697-701.
6. Guglielmetti, S., J.K. Dart, and V. Calder, Atopic keratoconjunctivitis and atopic dermatitis. *Curr Opin Allergy Clin Immunol*, 2010. 10(5): p. 478-85.
7. Boboridis, K., N. Kozeis, and A.G.P. Konstas, Revisiting Ocular Allergy: Evaluating symptoms, Benzalkonium Chloride and efficacy of topical Ketotifen 0,025%. *Ocul Immunol Inflamm*, 2018.
8. Hollo, G., et al., Preservative-Free Prostaglandin Analogs and Prostaglandin/Timolol Fixed Combinations in the Treatment of Glaucoma: Efficacy, Safety and Potential Advantages. *Drugs*, 2018. 78(1): p. 39-64.
9. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*, 2007. 5(2): p. 75-92.
10. Craig, J.P., et al., TFOS DEWS II Definition and Classification Report. *Ocul Surf*, 2017. 15(3): p. 276-283.
11. Shimazaki, J., et al., Meibomian gland dysfunction in patients with Sjogren syndrome. *Ophthalmology*, 1998. 105(8): p. 1485-8.
12. Baudouin, C., (A new approach for better comprehension of diseases of the ocular surface). *J Fr Ophtalmol*, 2007. 30(3): p. 239-46.
13. Luo, L., et al., Hyperosmolar saline is a proinflammatory stress on the mouse ocular surface. *Eye Contact Lens*, 2005. 31(5): p. 186-93.
14. Kunert, K.S., A.S. Tisdale, and I.K. Gipson, Goblet cell numbers and epithelial proliferation in the conjunctiva of patients with dry eye syndrome treated with cyclosporine. *Arch Ophthalmol*, 2002. 120(3): p. 330-7.
15. Baudouin, C., et al., Revisiting the vicious circle of dry eye disease: a focus on the pathophysiology of meibomian gland dysfunction. *Br J Ophthalmol*, 2016. 100(3): p. 300-6.
16. Arita, R., et al., Meibomian gland duct distortion in patients with perennial allergic conjunctivitis. *Cornea*, 2010. 29(8): p. 858-60.
17. Na, K.S., et al., The Influence of Overnight Orthokeratology on Ocular Surface and Meibomian Glands in Children and Adolescents. *Eye Contact Lens*, 2016. 42(1): p. 68-73.
18. Hom, M.M., A.L. Nguyen, and L. Bielory, Allergic conjunctivitis and dry eye syndrome. *Ann Allergy Asthma Immunol*, 2012. 108(3): p. 163-6.
19. Kumar, N., et al., Seasonal Variation in Dry Eye. *Ophthalmology*, 2015. 122(8): p. 1727-9.
20. Paulsen, A.J., et al., Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. *Am J Ophthalmol*, 2014. 157(4): p. 799-806.
21. Leonardi, A., The central role of conjunctival mast cells in the pathogenesis of ocular allergy. *Curr Allergy Asthma Rep*, 2002. 2(4): p. 325-31.
22. Hu, Y., et al., The differences of tear function and ocular surface findings in patients with atopic keratoconjunctivitis and vernal keratoconjunctivitis. *Allergy*, 2007. 62(8): p. 917-25.
23. Chidi-Egboka, N.C., et al., The ocular surface in children: A review of current knowledge and meta-analysis of tear film stability and tear secretion in children. *Ocul Surf*, 2019. 17(1): p. 28-39.
24. Boboridis, K.G. and A.G.P. Konstas, Evaluating the novel application of cyclosporine 0.1% in ocular surface disease. *Expert Opin Pharmacother*, 2018. 19(9): p. 1027-1039.
25. Wolffsohn, J.S., et al., TFOS DEWS II Diagnostic Methodology report. *Ocul Surf*, 2017. 15(3): p. 539-574.
26. Prince, A., M.R. Norris, and L. Bielory, Seasonal ocular allergy and pollen counts. *Curr Opin Allergy Clin Immunol*, 2018. 18(5): p. 387-392.
27. Doan, S. and Sécheresse oculaire : quelles causes ?, in *La sécheresse oculaire de la clinique au traitement*. 2008, Editions MED'COM.: Paris, France. . p. 21-24.

28. De Paiva, C.S. and E.M. Rocha, Sjogren syndrome: what and where are we looking for? *Curr Opin Ophthalmol*, 2015. 26(6): p. 517-25.
29. Fraunfelder, F.T., J.J. Sciubba, and W.D. Mathers, The role of medications in causing dry eye. *J Ophthalmol*, 2012. 2012: p. 285851.
30. Marshall, L.L. and J.M. Roach, Treatment of Dry Eye Disease. *Consult Pharm*, 2016. 31(2): p. 96-106.
31. Mateo Orobia, A.J., et al., Combination of hyaluronic acid, carmellose, and osmoprotectants for the treatment of dry eye disease. *Clin Ophthalmol*, 2018. 12: p. 453-461.
32. Ang, B.C.H., et al., Sodium Hyaluronate in the Treatment of Dry Eye Syndrome: A Systematic Review and Meta-Analysis. *Sci Rep*, 2017. 7(1): p. 9013.
33. Chiambaretta, F., et al., A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. *Eur J Ophthalmol*, 2017. 27(1): p. 1-9.
34. Fariselli, C., et al., Trehalose/hyaluronate eyedrop effects on ocular surface inflammatory markers and mucin expression in dry eye patients. *Clin Ophthalmol*, 2018. 12: p. 1293-1300.
35. Doan, S., D. Bremond-Gignac, and F. Chiambaretta, Comparison of the effect of a hyaluronate-trehalose solution to hyaluronate alone on Ocular Surface Disease Index in patients with moderate to severe dry eye disease. *Current Medical Research and Opinion*, 2018. 34(8): p. 1373-1376.
36. Fondi, K., et al., Effect of Hyaluronic Acid/Trehalose in Two Different Formulations on Signs and Symptoms in Patients with Moderate to Severe Dry Eye Disease. *J Ophthalmol*, 2018. 2018: p. 4691417.
37. Baudouin, C., et al., Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res*, 2010. 29(4): p. 12-34.
38. Tear-Film-and-Ocular-Surface-Society, INTERNATIONAL DRY EYE WORKSHOP (DEWS). *The Ocular Surface*, 2007. 5(2).
39. Coroi, M.C., S. Bungau, and M. Tit, PRESERVATIVES FROM THE EYE DROPS AND THE OCULAR SURFACE. *Rom J Ophthalmol*, 2015. 59(1): p. 2-5.
40. Nye, M., S. Rudner, and L. Bielory, Emerging therapies in allergic conjunctivitis and dry eye syndrome. *Expert Opin Pharmacother*, 2013. 14(11): p. 1449-65.
41. Bielory, B.P., T.P. O'Brien, and L. Bielory, Management of seasonal allergic conjunctivitis: guide to therapy. 2012. 90(5): p. 399-407.
42. Castillo, M., et al., Topical antihistamines and mast cell stabilisers for treating seasonal and perennial allergic conjunctivitis. *Cochrane Database of Systematic Reviews*, 2015(6).
43. Carr, W., J. Schaeffer, and E. Donnenfeld, Treating allergic conjunctivitis: A once-daily medication that provides 24-hour symptom relief. *Allergy Rhinol (Providence)*, 2016. 7(2): p. 107-14.
44. Mortemousque, B., et al., Comparison of preservative-free ketotifen fumarate and preserved olopatadine hydrochloride eye drops in the treatment of moderate to severe seasonal allergic conjunctivitis. *J Fr Ophtalmol*, 2014. 37(1): p. 1-8.
45. Leonardi, A., et al., Efficacy and Tolerability of Ketotifen in the Treatment Of Seasonal Allergic Conjunctivitis: Comparison between Ketotifen 0.025% and 0.05% Eye Drops. *Ocul Immunol Inflamm*, 2018: p. 1-5.
46. Bouhlal, H., et al., (N acetyl-aspartyl glutamic acid (NAAGA) inhibits the adhesion of leukocytes to activated endothelial cells and down-modulates the cytokine-induced expression of adhesion molecules). *J Fr Ophtalmol*, 2002. 25(10): p. 993-1000.
47. Leonardi, A., et al., Clinical and biological efficacy of preservative-free NAAGA eye-drops versus levocabastine eye-drops in vernal keratoconjunctivitis patients. *Br J Ophthalmol*, 2007. 91(12): p. 1662-6.
48. Brignole-Baudouin, F., et al., (Evaluation of NAAGA efficacy in dry eye syndrome). *J Fr Ophtalmol*, 2009. 32(9): p. 613-20.
49. Bielory, L., et al., An algorithm for the management of allergic conjunctivitis. *Allergy Asthma Proc*, 2013. 34(5): p. 408-20.
50. Daniel, B.S. and D. Orchard, Ocular side-effects of topical corticosteroids: what a dermatologist needs to know. *Australas J Dermatol*, 2015. 56(3): p. 164-9.
51. Bielory, L., Allergic conjunctivitis: the evolution of therapeutic options. *Allergy Asthma Proc*, 2012. 33(2): p. 129-39.
52. Ozcan, A.A., T.R. Ersoz, and E. Dulger, Management of severe allergic conjunctivitis with topical cyclosporin a 0.05% eyedrops. *Cornea*, 2007. 26(9): p. 1035-8.
53. Wan, K.H.-N., et al., Topical Cyclosporine in the Treatment of Allergic Conjunctivitis. *Ophthalmology*, 2013. 120(11): p. 2197-2203.
54. Awan, M.A., et al., Penetration of topical and subconjunctival corticosteroids into human aqueous humour and its therapeutic significance. *British Journal of Ophthalmology*, 2009. 93(6): p. 708.



Théa Medical Library Collection



Laboratoires Théa
12 Rue Louis Blériot - ZI du Brézet
63017 Clermont-Ferrand cedex 2 - France
Tel. : +33 473 98 14 36 - Fax : +33 473 98 14 38
www.laboratoires-thea.com