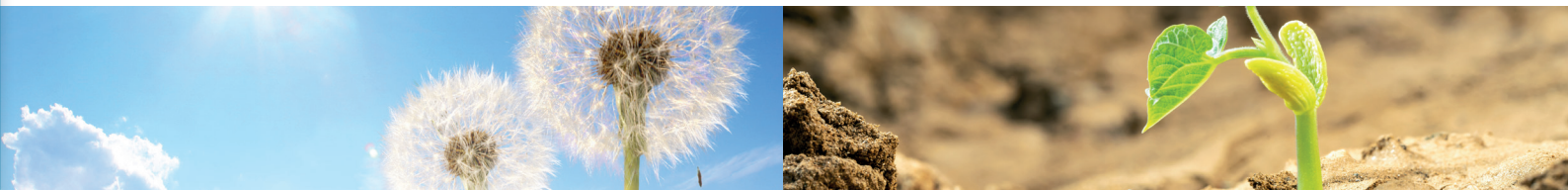


# Allergy & Dry Eye

OCULAR ALLERGY  
AND DRYNESS:  
A COMPREHENSIVE  
INTERRELATION







Ocular allergy and dry eye disease (DED) are common conditions, with a prevalence greater than 20%<sup>1,5</sup>. Both conditions can adversely affect patient health, patient-related quality of life, and decrease productivity, resulting in an economic burden to the patient and society at large<sup>2,4</sup>. Although clinically different, the signs and symptoms of ocular allergy and DED partially overlap, presenting a diagnostic challenge<sup>1,2,6</sup>. Hence, differentiating between ocular allergy and DED is imperative for prescribing the most appropriate therapy for the specific ocular surface disorder.



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## ■ ABBREVIATIONS

**AKC:** Atopic keratoconjunctivitis

**BAK:** Benzalkonium chloride

**CBC:** Contact blepharoconjunctivitis

**DED:** Dry Eye Disease

**GPC:** Giant papillary conjunctivitis

**IgE:** Immunoglobulin E

**NAAGA:** N-Acetyl Aspartyl Glutamic Acid

**OSD:** Ocular Surface Damage

**PAC:** Perennial Allergy Conjunctivitis

**SAC:** Seasonal Allergy Conjunctivitis

**TBUT:** Tear Break-Up Time

**VKC:** Vernal keratoconjunctivitis



# 1 Overview of ocular allergy

## ■ Definition and classification of ocular allergy

Ocular allergy is a common hypersensitivity disorder that affects 15%-20% of the population in developed nations<sup>3</sup>. This disorder can be divided into several categories:

- Allergic conjunctivitis, common, including seasonal and perennial forms (SAC and PAC, respectively). Seasonal allergy conjunctivitis (SAC) and perennial allergy conjunctivitis (PAC) are mild-to-moderate allergic disease, often associated with rhinitis, involving an IgE-mediated hypersensitivity response<sup>4</sup>.
- Keratoconjunctivitis, rarer, including vernal and atopic forms (VKC and AKC, respectively). Vernal keratoconjunctivitis (VKC) and Atopic keratoconjunctivitis (AKC) are severe chronic inflammatory diseases of the ocular surface with a more complex pathogenesis that includes a T-helper-mediated response<sup>4</sup>.
- Ocular toxicity-drug related allergy, which comprises chemical irritation of the ocular tissues, delayed (cell-mediated) hypersensitivity and a dose-dependent toxic response to a topically applied ophthalmic medication, leading to ocular surface changes. For example, preservatives such as benzalkonium chloride (BAK), a quaternary ammonium molecule, have a strong detergent effect on lipids and cell membranes<sup>6</sup>.

Figure 1 below summarizes the different types of ocular allergies and their specific characteristics on the ocular surface<sup>8</sup>:

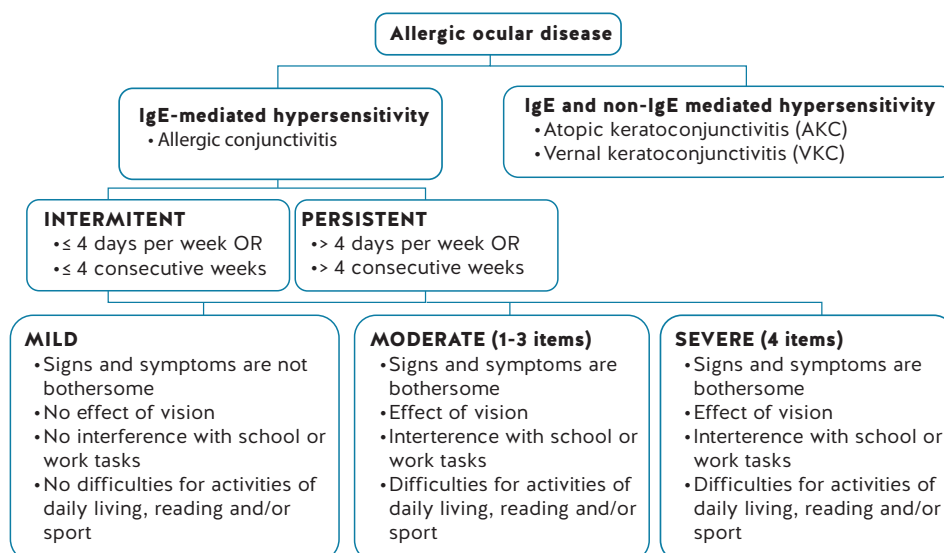


Figure 1: Classification of allergic ocular disease<sup>8</sup>

## ■ Patients affected by ocular allergy<sup>9,11</sup>

- Generally, children and adolescents are more commonly affected by atopic disease which tends to diminish with age.
- Individuals with asthma, eczema, and rhinitis often experience concurrent ocular

allergy. Europe, North America and Japan report higher prevalences than developing countries.

## ■ Manifestation and etiology

- Ocular allergy symptoms are often, but not always, associated with other allergic manifestations, mostly rhinitis<sup>10,11</sup>.
- The most common patient symptoms with all forms of ocular allergy are ocular itching, swelling, and tearing, whereas photophobia and intense itching are typical of the most severe disease due to frequent corneal involvement (in up to 70% of patients), ranging from superficial punctate keratitis to ulcers and plaques<sup>4</sup>. Symptoms may occur as acute episodes that are generally recurrent or may persist as chronic disease<sup>11</sup>.
- Based to the triggering allergen and the season, symptoms can be seasonal, frequent or perennial. Disease exacerbation can be triggered either by allergen re-exposure or, more frequently, by nonspecific stimuli such as sunlight, wind, and dust<sup>10-12</sup>.
- The diagnosis of ocular allergy is usually based on clinical history and signs and symptoms, with *in vivo* and *in vitro* tests when the identification of a specific allergen is required due to sensitization and for appropriate patient management<sup>11</sup>.

The nomenclature for ocular allergy is based either on clinical signs and symptoms (Table 1) or on pathophysiology, according to the different hypersensitivity mechanisms introduced by Gell and Coombs<sup>11</sup>.

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

Table 1: Main features of ocular allergies<sup>8,11</sup>

CBC denotes contact blepharoconjunctivitis; GPC denotes giant papillary conjunctivitis

## ■ Diagnosis of ocular allergy

When the patient initially visits, three types of diagnostic investigations are employed, especially when the history, signs, and symptoms indicate an ocular allergic disease<sup>11</sup>.

**History and symptoms:** the patient should be queried on itching, the type of discharge, duration of symptoms, and exacerbating factors. Bilateral symptoms typically suggest an infective or allergic cause, although both can manifest asymmetrically. Red, watery, and itchy eyes recurring in the spring and summer is highly suggestive of allergic eye



disease. Nasal symptoms might be present. A history of atopic disease such as eczema or asthma favours an allergic cause<sup>8,10,11</sup>.

**Signs:**

- Assess visual acuity using the Snellen chart.
- Examine the lids for swelling and dermatitis.
- Use a torch, preferably with a magnifier, to assess for conjunctival redness or swelling and any obvious corneal or limbal irregularities. Subtarsal upper lid papillae are often present. Topical fluorescein may show signs of keratitis and can be used in primary care for any red eye associated with pain, loss of vision or photophobia<sup>8,9</sup>.

## 2 Overview of dry eye disease

### ■ Definition and classification of dry eye

- Dry Eye Disease (DED) is defined as a multifactorial disease of the tears and ocular surface that results in symptoms including discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and subacute inflammation of the ocular surface<sup>13</sup>.
- DED is a common disease with a global prevalence varying from 5% to 34%. It is clinically subdivided into two subtypes<sup>13,14</sup>:
  - » Aqueous-deficient DED with decreased tear secretion,
  - » Evaporative DED with increased tear evaporation.

### ■ Manifestation and etiology<sup>14</sup>

The pathogenetic mechanisms of dry eye include hyperosmolarity of the tear film and inflammation of the ocular surface and lacrimal gland. The subjective symptoms in DED are often nonspecific and include<sup>14</sup>:

- Redness,
- Burning,
- Stinging,
- Foreign body sensation,
- Pruritus,
- Photophobia.

Many factors may favor progression of DED and then, increase clinical symptoms.

• High level of evidence	• Moderate level of evidence	• Low level of evidence
<ul style="list-style-type: none"> <li>• Age</li> <li>• Female sex</li> <li>• Postmenopausal estrogen therapy</li> <li>• Antihistamines</li> <li>• Collagen vascular disease</li> <li>• Corneal refractive surgery</li> <li>• Irradiation</li> <li>• Hematopoietic stem cell transplantation</li> <li>• Vitamin A deficiency</li> <li>• Hepatitis C</li> <li>• Androgen insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Medications such as tricyclic antidepressants,</li> <li>• Selective serotonin reuptake inhibitors,</li> <li>• Diuretics, beta-blockers</li> <li>• Diabetes mellitus</li> <li>• HIV/HTLV1 infection</li> <li>• Systemic chemotherapy</li> <li>• Cataract surgery with a large incision</li> <li>• Keratoplasty</li> <li>• Isotretinoin</li> <li>• Low air humidity</li> <li>• Sarcoidosis</li> <li>• Ovarian dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>• Smoking</li> <li>• Hispanic ethnicity</li> <li>• Anticholinergic drugs such as anxiolytics, antipsychotics</li> <li>• Alcohol</li> <li>• Menopause</li> <li>• Botulinum toxin injection</li> <li>• Acne</li> <li>• Gout</li> <li>• Oral contraceptives</li> <li>• Pregnancy</li> </ul>

Table 2: Risk factors for dry eye disease<sup>14</sup>

## ■ Diagnosis of dry eye disease<sup>14,15</sup>

The diagnosis of DED is based on signs and symptoms. The following 5 points summarize the main assessments for diagnosing DED.

- 1. Patient history, using a symptom-oriented questionnaire:** Several questionnaires exist such as the Ocular Surface Disease Index (OSDI), Dry Eye Questionnaire (DEQ-5), and Symptoms Assessment in Dry Eye (SANDE), and other survey instruments may be useful in assessing dry eye symptoms.
- 2. Tear film break-up time with fluorescein:** this is the interval of time between a complete blink and the first break in the tear film. It is most commonly performed in the clinic using a slit lamp after instilling sodium fluorescein stain to enhance the visibility of the tear film.
- 3. Ocular surface assessment with fluorescein/lissamine green staining:** Fluorescein staining allows assessment of corneal damage. Lissamine allows the assessment of conjunctival and lid margin damage, and to a lesser extent, corneal damage. The green points in Figure 2 are the "wounds" captured by the fluorescein, which turn blue with blue light.
- 4. Schirmer test with/without anesthesia:** Schirmer test is used to measure basic and reflex tearing with less than 5 to 10 mm (depending on the cut-off criteria) of wetting after 5 minutes diagnostic for aqueous deficiency (Figure 3).

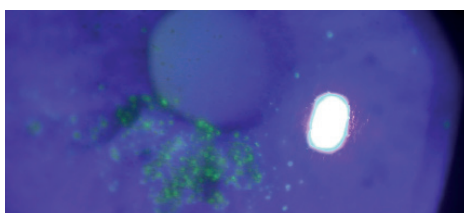


Figure 2: Ocular surface assessment with fluorescein green staining

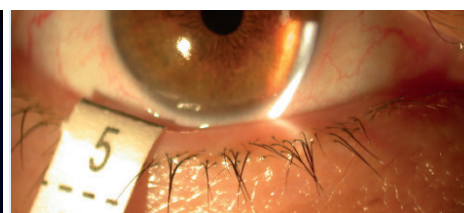


Figure 3: Schirmer test

## 3

# Ocular allergy associated to dry eye disease

**Allergy may be the underlying cause of dry eye.** Different studies suggest that the prevalence of DED has periodic pattern of presentation<sup>15-17</sup>. DED prevalence is higher during the spring (triggered by pollen, suggesting an allergic component) and winter (triggered by low humidity, suggesting dryness) compared to summer and fall. Perennial symptoms including itching, hyperemia and excess lacrimation, are attributed to indoor causes such as dust, mould, pet dander, etc.<sup>16-18</sup>.

**Hence, some experts consider ocular allergy a risk factor for DED<sup>16,19</sup>.**

The exposure to perennial allergens such as dust is associated to a significantly decreased of tear film break-up time which is an important objective sign of DED<sup>16</sup> (Figure 4).

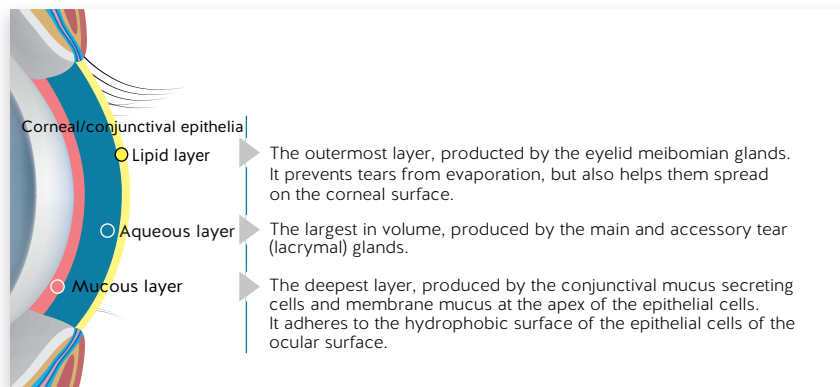


Figure 4: Layers of the tear film<sup>20</sup>

In ocular allergy, the cascade of events after exposure to allergens leads to cell damage followed by cell death via apoptosis. This leads to disruption of homeostasis, cell death, and inflammation creating a vicious cycle that promotes dryness and exacerbates clinical symptoms<sup>4</sup>. Hence, ocular allergy, particularly the severe forms of keratoconjunctivitis, can impact different key mechanisms of the vicious cycle of DED, including tear film instability, ocular surface inflammation and damage, and neurosensory abnormalities (Figure 5)<sup>4</sup>.

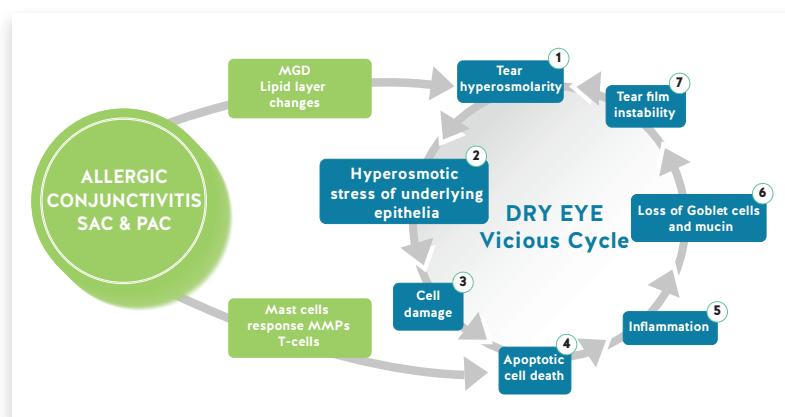


Figure 5: Allergy-mediated entry points into the vicious cycle of DED. SAC denotes seasonal allergic conjunctivitis; PAC denotes perennial allergic conjunctivitis<sup>20</sup>

# 4 How to distinguish ocular allergy from DED

Ocular allergy and DED are conditions that share common elements including signs and symptoms that affect the ocular surface. Since they share common clinical and biochemical features, a meticulous history-taking is imperative to differentiate between these conditions and establish an accurate diagnosis<sup>1,4,14</sup>.

The differentiation of the two diseases is based on the interrogation (clinical history), the clinical examinations (signs and symptoms), the causative factors, and complementary examinations (*in vivo* and *in vitro* tests)<sup>14</sup>.

## ■ Interrogation

• Ocular allergy evaluation <sup>4,8,11</sup>	• DED - Ocular Surface Disease Evaluation <sup>14,15,16,19,21</sup>
<ul style="list-style-type: none"> <li>• Frequent clinical association eye/nose</li> <li>• Shared pathophysiological mechanisms with allergic rhinitis</li> <li>• Same environmental exposure and triggers in common</li> <li>• Eyelid swelling on waking up. The presence of aqueous discharge in the morning are also indicative of allergy</li> <li>• Allergic eye disease is usually bilateral and itching is the predominant symptom</li> <li>• The presence of environmental triggers such as cosmetics, pets, seasonal pollen or domestic mites and dust can help establish the diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>• Difficulty opening eyes in the morning because of dryness during sleep (relatively specific)</li> <li>• Visual disturbance, such as intermittent blurry vision clearing with eye rubbing and functional disturbance may occur in daily activities such as computer use, book reading, and driving</li> <li>• Dryness of the mouth, skin or vagina is a fundamental symptom of DED suggesting systemic involvement, eg. Sjögren syndrome</li> <li>• Facial skin disorders such as acne, rosacea or seborrheic dermatitis may suggest meibomian gland dysfunction (MGD) and blepharitis</li> <li>• Hormone disorders or hormone replacement therapy during menopause and certain medications such as beta blockers, anticholinergic drugs, antidepressants or retinoids may elicit DED</li> </ul>

## ■ Clinical examination

• Signs of allergy <sup>8,9</sup>	• Signs of DED <sup>14</sup>	• Non-specific signs <sup>9</sup>
<ul style="list-style-type: none"> <li>• Assess visual acuity using a Snellen chart</li> <li>• Examine the lids for swelling and dermatitis</li> <li>• Use a torch, preferably with a magnifier, to assess for conjunctival redness or swelling and any obvious corneal or limbal irregularities</li> <li>• Subtarsal upper lid papillae are often evident</li> </ul>	<ul style="list-style-type: none"> <li>• Tear Film Break-up Time (TBUT): a cut-off of less than 10 seconds is often considered consistent with DED</li> <li>• The Schirmer I test is performed without topical anesthetic to measure basic and reflex tearing and values of 5 mm or less of wetting after 5 minutes is diagnostic for aqueous deficiency</li> <li>• Corneal and conjunctival damage: test with fluorescein and lissamine staining</li> <li>• Eyelid evaluation (blepharitis, lid wiper epitheliopathy, meibomian gland, etc.)</li> </ul>	<ul style="list-style-type: none"> <li>• Topical fluorescein can show signs of keratitis and can be used in primary care for any red eye associated with pain, loss of vision, or photophobia such as ocular allergy and dry eye</li> </ul>

## Etiology

The illustration below presents the different pathologies, classifications and underlying or concomitant conditions that may assist the practitioner in evaluating, diagnosing and managing the disease.

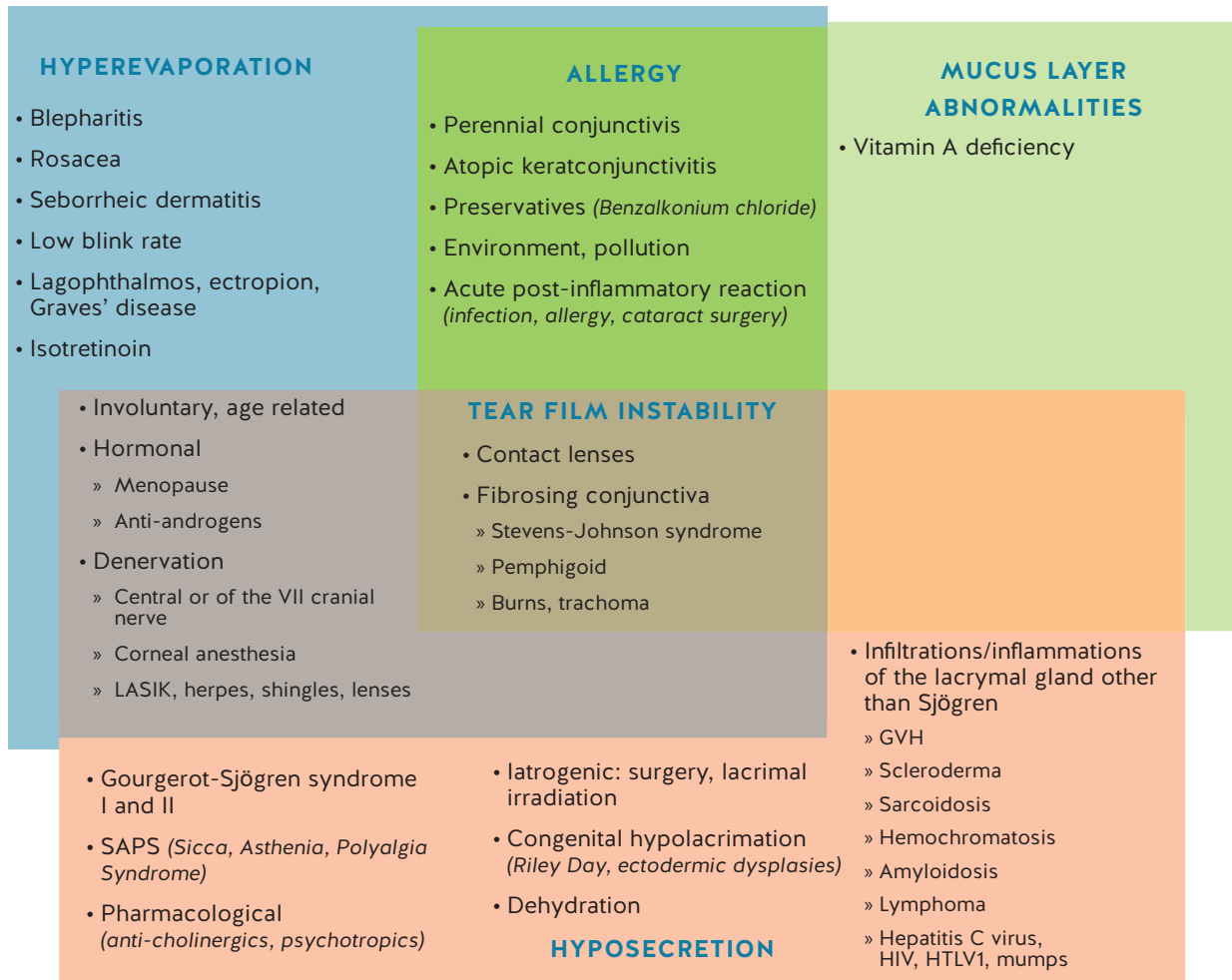


Figure 6: Causative factors of dry eye disease, adapted from Doan (2008)<sup>21</sup>

The following table presents the most common airborne and contact allergens leading to ocular allergy.

• AIRBORNE ALLERGENS	• CONTACT ALLERGENS
<p><b>Seasonal</b></p> <ul style="list-style-type: none"> <li>• Pollen (<i>trees, grasses, herbaceous plants</i>)</li> </ul> <p><b>Perennials</b></p> <ul style="list-style-type: none"> <li>• Dust mites (<i>dermatophagoides pteronyssinus</i>)</li> <li>• Mould</li> <li>• Animal dander (<i>cat, dog, etc.</i>)</li> </ul>	<p><b>Cosmetics</b></p> <ul style="list-style-type: none"> <li>• Make-up and cleansers</li> <li>• Nail polish</li> </ul> <p><b>Professionals</b></p> <ul style="list-style-type: none"> <li>• Resins, latex, etc.</li> </ul> <p><b>Topical treatments</b></p> <ul style="list-style-type: none"> <li>• Beta-blockers</li> <li>• Preservatives (<i>Benzalkonium chloride</i>)</li> </ul>

Table 3: Main categories of allergens associated with ocular allergy<sup>20</sup>.

# 5 Strategy for managing dry eye disease associated with ocular allergy

## ■ General considerations for ocular allergy and dry eye disease management<sup>20</sup>

An effective approach to the general macro-management of ocular allergies leading to ocular surface disease such as dry eye, must aim 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 meibomian gland dysfunction and reverse the ocular surface damage (Figure 7).

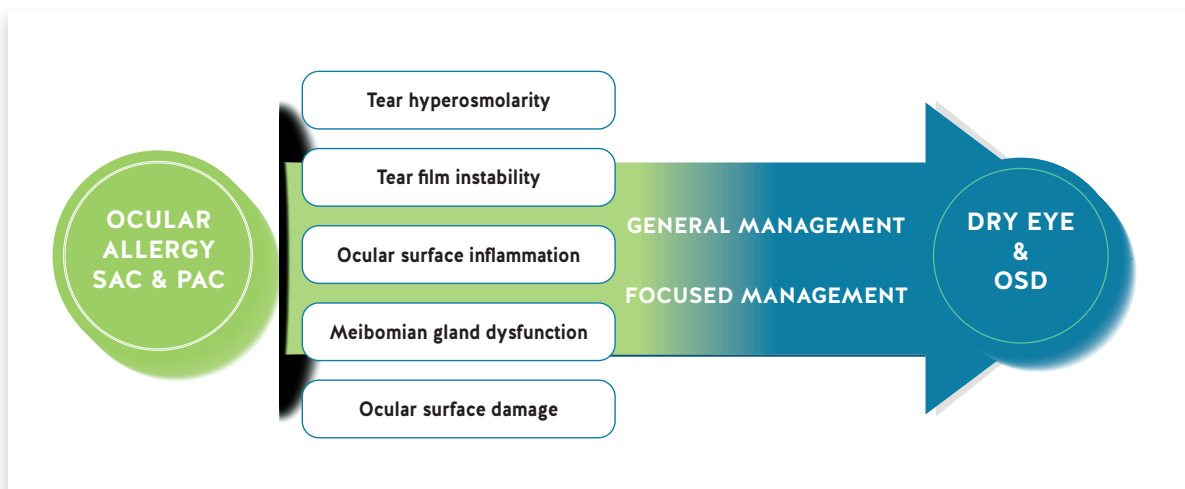


Figure 7: The management of allergic conjunctivitis [seasonal allergic conjunctivitis (SAC) or perennial allergic conjunctivitis (PAC)] for alleviating the effects of ocular allergy on dryness includes general, environmental and lifestyle modifications, symptom relief products such as trehalose and hyaluronic acid containing artificial tears and targeted pharmacological management to address more severe conditions<sup>20</sup>.

## ■ General management: the initial measures<sup>11,12</sup>

Patients suffering from seasonal or perennial allergic conjunctivitis (SAC or PAC, respectively) and mild dry eye symptoms can be affected by several exacerbating factors that are generally environmental or lifestyle-related. For SAC and PAC, patients should be advised to avoid contact with potential allergens such as pollen, dust mites, animal

ander, mould spores and local irritants (Figure 8). The conventional lifestyle modifications for the management of dryness in allergy are focused on avoiding factors that may exacerbate dry eye symptomatology as described in the figure below (Figure 8)<sup>9,20</sup>.



Figure 8: Primary measures and lifestyle interventions for managing allergic conjunctivitis and related dry eye. AC denotes air conditioning; AH denotes anti-histamines<sup>20</sup>.

## ■ General management: determining treatment<sup>9,15,22</sup>

There are 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 for greater tear retention and treating concomitant eyelid disorders such as MGD can also be considered (Figure 9).

Proposed general management for OSD <sup>(2, 8-11)</sup>	
<b>SUPPORT THE TEAR FILM</b>	<ul style="list-style-type: none"> <li>• Hyaluronic acid products</li> <li>• Osmoprotectants such as trehalose</li> <li>• Lipid-based eyedrops</li> </ul>
<b>PROTECT THE EPITHELIUM</b>	<ul style="list-style-type: none"> <li>• Hyaluronic acid products</li> <li>• Osmoprotectants such as trehalose</li> </ul>
<b>REDUCE INFLAMMATION</b>	<ul style="list-style-type: none"> <li>• Hyaluronic acid products</li> <li>• Osmoprotectants such as trehalose</li> <li>• Tetracyclins</li> <li>• Soft steroids</li> <li>• Cyclosporine drops</li> <li>• Azithromycin</li> <li>• NAAGA</li> </ul>
<b>NON PRESERVED SOLUTIONS</b>	<ul style="list-style-type: none"> <li>• Preservative-free ocular artificial tear solutions/gels/ointments</li> </ul>
<b>TREATING EYELID DISORDERS (MGD &amp; BLEPHARITIS)</b>	<ul style="list-style-type: none"> <li>• Eyelid hygiene - tea tree oil for demodex</li> <li>• Warm compresses and warming devices</li> <li>• Tetracyclins</li> <li>• Azithromycin</li> </ul>

Figure 9: General management of Ocular Allergy OSD<sup>9,15,20,22,23</sup>

## ■ General management: focus on preservative-free treatment

The toxicity of BAK and other preservatives has been well established<sup>24,25</sup>. Ophthalmic preservatives cause tear film instability, ocular surface changes, conjunctival inflammation, epithelial apoptosis and subconjunctival fibrosis<sup>24,25</sup>. Multiple studies have demonstrated a significant improvement in ocular toxicity with preservative-free ophthalmic solutions for the treatment of allergic conjunctivitis and other ocular diseases<sup>6,7</sup>.

Preservative-free formulations are of primary importance for cases of severe dry eye with ocular surface disease and impaired lacrimal gland secretion, cases of significantly decreased tear secretion, punctal occlusion and for patients on multiple preservative-containing topical medications for chronic ocular disease. Additionally, preservative-free formulations are necessary in patients with allergies to preservatives or epithelial toxicity due to preservatives<sup>26,27</sup>.

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

### • A KEY ROLE FOR PRESERVATIVE-FREE PRODUCTS<sup>26,27</sup>

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



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# Allergy & Dry Eye

OCULAR ALLERGY  
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A COMPREHENSIVE  
INTERRELATION

