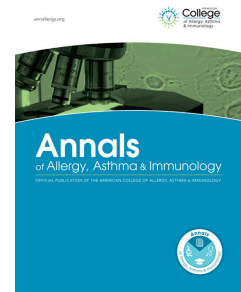


Journal Pre-proof

The spectrum of allergic ocular diseases-2020

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PII: S1081-1206(20)31220-5

DOI: <https://doi.org/10.1016/j.anai.2020.11.016>

Reference: ANAI 3431

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 13 July 2020

Revised Date: 23 November 2020

Accepted Date: 24 November 2020

Please cite this article as: Rodrigues J, Kalangara ME, Vanijcharoenkarn K, Patel N, Hom MM, Wallace DV, The spectrum of allergic ocular diseases-2020, *Annals of Allergy, Asthma and Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2020.11.016>.

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Title: The spectrum of allergic ocular diseases-2020

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- a. Conflicts of interest: none.**
- b. Funding Source: none**
- c. Trial Registration: not applicable**
- d. Key Words:**

- Allergic conjunctivitis
- Allergic rhinoconjunctivitis
- Atopic keratoconjunctivitis
- Contact blepharoconjunctivitis
- Dry eye disease
- Ocular allergy
- Ocular corticosteroids
- Sublingual immunotherapy
- Subcutaneous immunotherapy

- Vernal keratoconjunctivitis

e. Abbreviations:

- Atopic keratoconjunctivitis: AKC
- Chemoattractant receptor-homologous molecule expressed on TH2 cells: CRTH2
- Conjunctival provocation test: CPT
- Contact blepharoconjunctivitis: CBC
- Dry eye disease: DED
- Giant Papillary Conjunctivitis: GPC
- Intranasal steroids: INS
- Limbal stem cell deficiency: LCSD
- Mast cell: MC
- Perennial allergic conjunctivitis: PAC
- Prostaglandin D2: PGD2
- Seasonal allergic conjunctivitis: SAC
- Skin prick testing: SPT
- Slit lamp examination: SLE
- Subcutaneous immunotherapy: SCIT
- Sublingual immunotherapy: SLIT
- Total Ocular Symptom Score: TOSS
- Vernal keratoconjunctivitis: VKC

f. **Word count:** 5664

g. **Figures:** Figure 1

h. **Tables:**

Table 1: Classification and Clinical Features of Ocular Allergic Diseases

Table 2: Differential diagnosis of ocular allergy – demographics and symptomatology

Table 3: Differential diagnosis of ocular allergy – physical findings

Table 4: Total Ocular Symptom Score (TOSS) questionnaire

Table 5: Preservative-free ocular lubricants and selected artificial tears by viscosity

Table 6: Ocular Medications – Decongestants, Antihistamines and Multi-action

Table 7: Ocular Medications –Mast cell stabilizers, NSAIDs, steroids and calcineurin inhibitors

20-07-0450R2

Objective: The purpose of this paper is to review the pathophysiologic mechanisms, differential diagnosis, evaluation and treatment of the various manifestations of ocular allergy, with an especial focus on IgE-mediated disease.

Data Sources: A PubMed search was performed to include articles with the search terms ocular allergy and allergic conjunctivitis.

Study Selections: Recent and relevant human studies in the English language pertaining to our topic of study were selected. Animal studies pertaining to pathophysiology of ocular allergy were also reviewed. We focused on clinical trials, practice guidelines, reviews and systematic reviews. Additionally, case reports were reviewed if they described rare clinical presentations, disease mechanisms or novel therapies.

Results: Ocular allergy encompasses both IgE as well as non-IgE mediated disease, and the clinical severity may range from mild to sight-threatening inflammation. A comprehensive treatment regimen including education, lifestyle measures, topical therapies and even systemic interventions may be necessary for the effective management of ocular allergies, tailored according to symptom severity.

Conclusion: Ocular allergy is frequently encountered by allergists as well as eye-care specialists, and despite progressively increasing incidence, it often remains underdiagnosed and hence untreated.

1 • **Introduction:**

2 Ocular manifestations of allergic disease were first described in 1819 by John Bostock, when he
3 detailed the case of a 46-year-old male who experienced eye redness, itching and watery
4 discharge from June to August every year.¹ Over the past 200 years, our understanding of ocular
5 allergy has evolved and is now recognized as a heterogeneous collection of IgE and non-IgE
6 mediated diseases. A thorough ocular evaluation is essential for these diagnoses, ideally
7 involving collaboration between the allergist and eye-care specialist.

8
9 • **Epidemiology:**

10 The accurate determination of ocular allergy prevalence is confounded by varying definitions
11 and multiple questionnaires used for assessment. One review cites the global prevalence of
12 ocular allergy at 6.4–7.1%.² Another source approximates that of the 15-20% of the world
13 population who are atopic, 40-60% experience ocular symptoms.³ In yet another study of 187
14 allergic rhinitis patients, 95% reported ocular allergy.⁴ In the US, ocular allergy affects an
15 estimated 36% of the population⁵, with an over 3-fold increase in a 20-year period.^{5,6} Warm
16 climates appear to pose a higher risk for ocular allergy.⁷ Patients over 50 years also reported
17 increased frequency of isolated ocular symptoms, while younger patients tend to have combined
18 naso-ocular symptoms. Particular allergens, such as animals, house dust mite, and pollen, also
19 appear to increase ocular compared to nasal symptoms.⁵

20 Ocular allergies are frequently under-reported, possibly due to symptom variability, acceptance
21 of symptoms as “normal”, and a heightened focus on nasal and other non-ocular symptoms.⁷

22 Despite under-reporting, allergic conjunctivitis is significantly detrimental to quality of life. A
23 survey of allergic rhino-conjunctivitis patients (n=2,765) rated red/itchy eyes as the second-most

“extremely bothersome” symptom after nasal congestion.⁸ Furthermore, in a cross-sectional study of allergic rhinitis patients (n=2,150), conjunctival symptoms conferred an increased risk of asthma.⁹

- **Classification:**

While many methods have been proposed to classify ocular allergies, the most commonly used classification organizes ocular surface hypersensitivity disorders into ocular allergy and non-allergic hypersensitivity.¹⁰ Ocular allergy, an IgE or non-IgE-mediated disease process, includes seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and contact blepharoconjunctivitis (CBC). SAC and PAC account for the majority (95-98%) of ocular allergy, while AKC and VKC represent an estimated 2% of all ocular allergies.⁷ VKC, despite accounting for 0.1–0.5% of ocular allergy in developed countries, is more prevalent in sub-tropical, underdeveloped countries (around 4% in African children).¹¹ VKC and AKC involve both IgE and non-IgE mediated mechanisms. **Table 1** compares the major characteristics associated with these disorders.

- **Clinical Entities:**

SAC and PAC are caused by allergen-induced, IgE-mediated reactions. SAC is intermittent while PAC is persistent. Patients present with conjunctival redness, itching, chemosis, and eyelid swelling.^{7,10} In the US, SAC is triggered by tree and grass pollen in the spring and summer, respectively, while weed pollen, especially ragweed, predominates in the fall. PAC is caused by

perennial allergen exposure, such as dust mite, animals, or polysensitization. Patients have persistent symptoms year-round, with exacerbations secondary to increased allergen or irritant exposure.¹⁰ The most prevalent allergens can differ by season as well as geographic region, likely due to the differences in climate¹². Neither entity has corneal involvement.

VKC classically occurs in warmer climates, predominantly affecting boys aged 4-12 years, usually resolving in puberty. It is rare in North America, with a prevalence of 1 for every 5000 cases of ocular disease. While there is a male: female ratio of 3:1 in children, this transitions to 1:1 when symptoms persist into adulthood. Symptoms include intense ocular pruritus, irritation, mucoid discharge, red eyes, and photophobia. Papillae size in VKC can range from 0.1 mm to giant cobblestone papillae as large as 5 mm and based on location, VKC is classified into tarsal, limbal or mixed^{13,14}. VKC is a severe persistent form of ocular allergy, and can be sight-threatening if untreated. VKC is both IgE and non-IgE mediated (T-cell and eosinophil infiltration). Exacerbations are triggered by allergen re-exposure as well as irritants. VKC flares can lead to corneal erosions, ulcers and scars in 30% patients.¹⁵

AKC is among the most severe ophthalmic complications of atopic dermatitis.¹⁶ It presents with bilateral inflammation of the eyelids, cornea, and conjunctiva. Among patients with atopic dermatitis, its prevalence is variably estimated to be 20-77%.^{17,18} AKC usually begins in young adulthood, and peaks between 30-50 years with a M:F ratio of 2.4:1.¹⁹ An eczematous patch usually starts on the eyelid, leading to thickening and fissuring of the skin. Conjunctival micropapillae with intense infiltrate can be seen early in disease, which can progress to giant macropapillae and even diffuse conjunctival scarring^{20,21}. Infections with *staphylococcus aureus* can also occur, accompanied by Meibomian gland dysfunction. Chemosis is usually noted in the inferior conjunctival fornix and the palpebral conjunctiva. The cornea and limbus can also be

involved. In atopic dermatitis patients, the presence of ocular pain, photophobia, visual changes, and giant papillae in the inferior fornix should raise suspicion for AKC. This diagnosis poses a higher risk of corneal injuries and severe sequelae than other ocular allergies. Complications include keratoconus, conjunctival fibrosis, herpes simplex keratitis, retinal detachment, and cataracts, all of which can be sight-threatening.¹⁰

CBC is a non-IgE mediated allergic contact dermatitis of the eyelids with or without extra-ocular dermatitis. Cosmetics, metals and eye medications are the most common agents causing CBC²². While 15-20% of the population will experience contact dermatitis, approximately 50% of which is related to type IV hypersensitivity, it is estimated that 5.7% have exclusively eyelid dermatitis.^{23,24} CBC patients are twice as likely to be female and usually middle-aged or older.²³ While the conjunctiva may be involved, almost all patients will present with eyelid dermatitis, itching and burning being the main symptoms. CBC should also be considered in non-atopic patients who present with ocular itching/burning and eyelid dermatitis.

- **Pathogenesis:**

While the role of T-helper 2 (Th2) responses is established in ocular allergy, recent evidence implicates additional mechanisms (Figure 1A). These mostly derive from mouse models, and are, therefore, of unclear relevance.

- o **Th2-mediated responses:**

Mast cells (MCs) are critical in ocular allergy, evidenced by absence of symptoms in MC-deficient mice.²⁵ SAC and PAC result from classic type I hypersensitivity, whereby allergen-complexed IgE binds the high affinity Fc-epsilon receptor I (FcεRI) on MCs with consequent

mediator release. The largest contributors to disease severity are allergen load on the ocular surface and local IgE production, as well as tear IgE levels.²⁶

Little is known about the late phase reaction prominent in chronic ocular allergy, especially VKC and AKC. The Th2 cytokines IL-4, IL-5 and IL-13 induce B-cell activation and IgE production, eosinophilic infiltration and mucus production. CD11b⁺ dendritic cells play a key role in Th2-driven ocular allergy.²⁷ MC mediators also contribute to late-phase inflammation with upregulation of adhesion molecules that mediate conjunctival accumulation of eosinophils, neutrophils, basophils and T-cells.²⁸ The degree of cellular infiltration correlates with disease severity.

o Alternative T-helper cell pathways:

The principal Th1 cytokine IFN- γ is elevated in tear cytokine profiles during the delayed phase at 24-48 hours following allergen exposure.²⁹ IFN- γ has been linked with chronic and severe forms of AC. The role of Th17 cells is poorly defined.³⁰

o Ocular surface barrier dysfunction:

Chronic ocular allergy is associated with barrier dysfunction and tear film instability, which may result in corneal damage.³¹ Histamine and Th2 cytokines, particularly IL-13, directly activate conjunctival goblet cells and drive mucin secretion.³² Downregulation of the major protective ocular mucin MUC5AC is seen in severe cases, with increase in other goblet cell mucins that may contribute to symptoms.³³

o Tissue remodeling in severe disease:

The formation of giant papillae distinguishes VKC and AKC, and consist of conjunctival epithelium, activated fibroblasts and an inflammatory cell infiltrate. Their mechanism of

formation is unclear. IL-13 stimulates periostin production from tissue fibroblasts and activates epithelial cells as well as fibroblasts. Copious amounts of periostin have been demonstrated in tears from patients with ocular allergy, particularly AKC, and strongly correlated with tear IL-13 levels.³⁴ Significant deposits of periostin have also been found within the papillae.³⁵

- **Clinical manifestations:**

Symptoms of ocular allergy

Four cardinal symptoms characterize ocular allergies: redness, itchiness, swelling, and watering (tearing).

Many ocular allergy symptoms overlap with those of dry eye, with over 50% of ocular allergy patients also having dry eyes.³⁶ One possible explanation would be that the concentration of inflammatory factors increases when the tear volume decreases in dry eyes.³⁷

Signs of ocular allergy:

Signs of ocular allergy are documented in **Table 1**. Eye-care specialists commonly perform a slit lamp biomicroscope exam (SLE) and fluorescein stain for examination. The SLE magnifies ocular structures and can change the lighting by varying size, brightness and angle of illumination. Fluorescein stain applied to the ocular surface allows detection of damage that appears as yellow areas or dots of staining. Corneal conditions and conjunctival papillae appear much more pronounced with fluorescein staining.³⁸

An adequate external eye exam can be accomplished with just a penlight. Depressing the lower lid and examining the palpebral conjunctiva can detect large conjunctival papillae (Figure 1 C-

E). Papillae can also be seen on the caruncle.³⁹ Hyperemia of the eye can also be observed with the naked eye (Figure 1 B). Hyperemia in one sector can be missed if the patient is looking straight ahead. Having the patient look in different directions while manipulating the lid to reveal more of the conjunctiva is helpful in detecting unseen redness.

- **Differential diagnosis of ocular allergy:**

The differential diagnosis of ocular allergy includes allergic and non-allergic, acute and chronic disorders. Based upon the history, the clinician is often asked to determine if the “red eye” causing the patient’s distress is likely to be allergic versus non-allergic. In the setting of red, itchy eyes and concomitant allergic nasal symptoms, SAC and PAC should be the diagnoses first considered. Many non-allergic disorders share similar characteristics and may co-exist, e.g., SAC/PAC and dry eye syndrome. Key ocular allergic conditions have been previously described. Non-allergic ocular disorders may also present with “red eye” and/or ocular itching, irritation, pain, or photophobia. The most common differentials are outlined in **Tables 2 and 3**.

Giant papillary conjunctivitis (GPC), an ocular non-allergic hypersensitivity, occurs due to repeated mechanical irritation by a foreign body such as contact lenses with resultant conjunctival inflammation. Atopy and aeroallergens do not play a role in pathogenesis but GPC is predominant in the atopic population and peaks in spring and fall. Thus, underlying SAC may be a risk factor for GPC.⁴⁰ GPC develops in 1-5% of soft contact lens wearers, mostly adolescents and young adults, and much less so with rigid, gas-permeable lenses. Infrequently, other foreign substances can trigger this disorder such as ocular prostheses and postoperative sutures. Symptoms include foreign body sensation, ocular itching, blurred vision, and increased mucus secretion.¹⁰ Cobblestoning of the upper bulbar conjunctiva produced by giant papillae 1-2 mm in size helps to establish this diagnosis.

Dry eye disease (DED) affects approximately 7% of adults but increases each decade reaching ~18% in those ≥ 75 years of age, with females affected twice as often as males.⁴¹ The most common cause is androgen deficiency, produced by menopause, aging, and antiandrogen therapy. Systemic and topical ocular medications; systemic diseases, e.g., diabetes, Sjogren syndrome; contact lens; ocular surgery and ocular allergy can all cause or contribute to DED⁴². While all patients with DED have tear film hyperosmolarity and ocular surface inflammation, patients often have predominantly either reduced tear production or increased evaporative loss⁴³. Symptoms include redness, dryness, excessive reflex tearing (due to irritation), gritty sensation, burning, and blurring of vision. Pruritus is notably absent. The diagnosis is most challenging when DED presents concurrently with or as a result of ocular allergy.

Infectious conjunctivitis is an acute onset, typically unilateral process, and can be either bacterial or viral. Purulent, sticky secretions, particularly upon awakening but continuing throughout the day, characterizes bacterial conjunctivitis. Watery discharge with minimal mucous and crusting is suggestive of a viral process, and may be accompanied by systemic symptoms of a viral infection.

Keratitis can be bacterial, most commonly found in contact lens wearers, or viral, e.g., herpes keratitis. It presents with a red eye, foreign body sensation, photophobia, and a corneal ulcer or infiltrate.

Scleritis is usually caused by underlying systemic inflammatory disease and presents with severe pain which radiates into the face, worse at night and early morning. Photophobia, redness, and watery discharge is often present.

Episcleritis predominantly affects middle-aged females and presents acutely with redness, watery discharge, and irritation with engorged blood vessels on a normal scleral background.

Episcleritis is painless and without visual impairment. More than 65% are isolated events but sometimes associated with DED or autoimmune disease, e.g., rheumatoid arthritis.⁴⁴

Iritis (anterior uveitis) is usually due to systemic infectious or immune-mediated disease, can be acute or insidious, and should be suspected with painful, isolated limbal redness associated and a constricted pupil.

Drug induced (toxic) conjunctivitis may be caused by active ocular medications but most commonly due to preservatives, such as benzalkonium chloride, thimerosal, parabens, ethylenediaminetetraacetic acid (EDTA) and chlorobutanol, in eye drops used longer than 3 months^{10,45,46}. Patients report initial improvement of eye symptoms with the medication, then worsening with continued use. Symptoms improve with discontinuation of culprit medications.

With the approval of dupilumab for the treatment of atopic dermatitis, a new type of drug-induced conjunctivitis has been described. New onset conjunctivitis has been reported to be increased in dupilumab-treated atopic dermatitis patients but not in asthmatics treated with dupilumab. Dupilumab induced conjunctivitis in atopic dermatitis patients has been observed in 9-28% of dupilumab 2-week clinical trials and also reported in 25-50% of patients in real-world observational studies⁴⁷⁻⁵¹. The exact pathogenesis remains unknown, although several possible mechanisms, e.g., early increase in blood eosinophils, increase in OX14 ligand activity, and increased IL-17 inflammation following colonization with demodex mites have been suggested⁵². IL-13 inhibition has been suggested to mediate goblet cell apoptosis and decrease mucin production, setting the stage for conjunctival inflammation⁵³. Also, interestingly, while IL-4 and IL-13 induce proliferation and mucin secretion by goblet cells, they also have a counter-regulatory role in blocking the increase in $[Ca^{2+}]_i$ mediated by histamine³². IL-4/IL-13 blockade may thus augment histamine induced mucus production following initiation of

dupilumab whereas pre-treatment, these cytokines were blocking histamine responses. Risk factors for dupilumab-induced conjunctivitis include severe atopic dermatitis, preexisting conjunctivitis, and low serum concentrations of dupilumab⁴⁹. Although non-specific, the most commonly reported symptoms are bilateral conjunctival hyperemia, pruritus, tearing, irritation, and foreign body sensation⁵⁴. The presenting signs are erythema of the bulbar and/or palpebral conjunctiva which is characteristically most severe in the limbal area⁴⁹. Blepharitis, usually mild, is also very common in these patients⁴⁹. Asymptomatic surface ocular disease has been noted on ophthalmological exam in up to 64% of these patients prior to the initiation of dupilumab⁵⁵. Dupilumab-induced conjunctivitis that is mild could usually be managed with warm compresses, ocular lubricants, antihistamine eye drops⁵⁴. Dupilumab induced conjunctivitis has been successfully treated with tacrolimus 0.03% eye ointment and fluorometholone 0.1% drops^{49,56}. Many times the treatment must be continued throughout the duration of dupilumab therapy. Therefore, when effective, tacrolimus 0.03% may be the safest long-term treatment, although in the US use of tacrolimus would be off-label for this indication⁴⁹. Patients with new-onset conjunctivitis while receiving dupilumab would benefit from referral to an eye-care specialist for further evaluation⁵⁴. Discontinuation of dupilumab while awaiting such evaluation is not necessary, unless the patient has signs of severe disease such as vision changes, eye pain and purulent discharge⁵⁴.

Corneal abrasion often due to contact lens or injury, presents with severe photophobia, watery discharge, pain, a strong foreign body sensation, and a constricted pupil.

Angle closure glaucoma is a rare cause of red eye. It is usually sudden in onset and associated with headache, nausea and vomiting. Finding a pupil fixed in mid-dilation and the distinctive ciliary flush help to confirm this ocular emergency.

- **Diagnosis:**

Detailed History:

A detailed history is essential to prevent misdiagnosis of sinister conditions causing “red eye” that have potential dire consequences such as vision loss. History taking should not only focus on eliciting symptoms, but should also evaluate laterality, duration, triggers, previous treatments, contact lens use, family history, comorbid asthma and/or allergic rhinitis, exposures (occupational, environmental and topical such as cosmetics) and history of ocular surgery, as these can be vital in making a diagnosis. Features such as unilateral disease, moderate-to-severe pain, purulent discharge and foreign body sensation especially in the elderly often suggest an alternate etiology and may warrant referral to an eye-care specialist.⁵⁷

Physical Exam:

The ocular signs of allergy are well-documented in **Table 1**. The physician should focus on the detection of papillae, hyperemia, venous congestion or “allergic shiners”, lid eczema, regional lymphadenopathy, all of which only require a simple external exam and a penlight. The SLE offers magnification of the ocular surface and fluorescein staining allows detection of damage to the ocular surface.

Testing Modalities:

Skin prick testing (SPT) is the first-line approach to diagnose IgE mediated sensitivity due to its sensitivity, efficacy, safety and feasibility.^{57,58} It should be performed for pollens, mites, animal

dander, and mold. Other allergens such as cockroach, latex and food allergens should be tested according to history and suspected exposures.¹⁰

Serum-specific IgE measurements should be considered when SPTs are inconsistent with the patient history, cannot be performed or to quantify specific IgE to naïve allergens. Component-resolved diagnosis may be helpful in the future for diagnosis in patients with multiple sensitizations. Total serum IgE is no longer considered necessary for diagnosis because normal values do not exclude an allergy diagnosis.¹⁰

Local procedures such as measurement of total tear IgE, tear specific IgE, tear fluid eosinophilia, and performing conjunctival scrapings or impression cytology can be used to grade disease severity or study ocular cytology, but are not routinely performed.⁵⁹⁻⁶¹ Conjunctival biopsies are only considered when neoplastic or autoimmune diseases must be ruled out.⁵⁹

Conjunctival provocation test (CPT), or conjunctival allergen challenge, involves the topical application of an allergen to the external ocular surface followed by assessment of the inflammatory response in a patient presumed to have ocular allergy.⁶² It helps ascertain the relevance of IgE-mediated sensitization detected via SPT or serum IgE testing, particularly when a patient is poly-sensitized. It is also useful when history is highly suggestive of ocular allergy but SPT and serum IgE testing are negative or inconclusive. CPT must be conducted out of season for the allergen of interest, on asymptomatic patients and in controlled settings by experienced staff. Two baseline visits are often used. At the first baseline visit, increasing doses of allergen extract are applied bilaterally into the conjunctival sac at 10-minute intervals. The patient is then observed for hyperemia, itching, chemosis, and lid swelling which is quantified according to a scale from 0 to 4. A threshold reaction of ≥ 2 is considered to reflect the severity of

allergic conjunctivitis in season. A second baseline visit a week later establishes reproducibility of the ocular reaction to the threshold dose of allergen extract.^{63,64} CPT is usually performed with a single allergen. Disadvantages include subjective testing parameters, lack of standardization/validation and inability to be performed in patients who have uncontrolled allergic disease, severe systemic diseases, patients who are pregnant or lactating or those who cannot interrupt the use of systemic/topical steroids or antihistamines.^{62,65} It has been suggested that systemic steroids be discontinued for 2-4 weeks and local corticosteroids for 1-4 weeks prior to CPT⁶². Following a positive CPT, the patient is usually observed for at least 2 hours, during which the conjunctival reaction, e.g. ocular erythema, pruritus and chemosis can be treated with cold compresses, vasoconstrictors, antihistamines, mast cell stabilizers and, if required, topical corticosteroids⁶². In the US, the CPT is infrequently used for the routine office-based diagnosis of ocular allergy and is predominantly reserved for use in research settings.

Patch testing can help evaluate non-IgE mediated sensitivity which may be causing peri-orbital dermatitis. The European battery or North American standard panel should be used as well as suspected cosmetics, ocular drugs or eye drop ingredients based on patient history.¹⁰

Advanced imaging techniques such as in vivo confocal microscopy, meibography, lipid layer interferometry and optical coherence tomography which enable the assessment of Meibomian gland structure, ocular surface lesions, tear film stability, lipid layer depth and corneal microstructure analysis are seldom used in diagnostic workup.⁵⁷

- **Scoring and grading ocular allergy:**

The four symptom domains of redness, itchiness, swelling, and watering (tearing) constitute an un-validated questionnaire called the Total Ocular Symptom Score (TOSS) which can be used for describing symptom severity and monitoring treatment response. (Table 4).^{66,67}

The only QoL questionnaire available to date for ocular allergy pertains selectively to VKC. The QoL in VKC children (QUICK) questionnaire grades frequency of ocular allergy on a 3-point scale (1=never, 2=sometimes, 3=always) to assess disease status.^{57,68} There is an unmet need to develop a QoL measure in ocular allergy as a whole to assess its effects across different subtypes and in all ages.

The ARIA workshop group suggested a severity classification of ocular allergy based on both persistence and severity of symptoms,⁶⁹ Persistence of symptoms was either classified as “intermittent” (lasting <4 days a week or <4 weeks a year) or “persistent” (symptoms lasting longer than intermittent symptoms). Severity of symptoms was graded as “mild”, “moderate” or “severe”, based on the presence or absence of visual disturbance, impairment of daily activities/school/work and troublesome symptoms.

- **Management:**

- 1. Avoidance and non-pharmacologic measures:**

Early detection of allergic triggers by SPT or sIgE testing and simple allergen avoidance measures such as eyewear barrier protection, frequent washing of clothes, hypoallergenic bedding and bathing/showering prior to bedtime, may all help to halt disease progression.⁷⁰ Avoidance of eye rubbing, cold compresses and refrigerated artificial tears may also provide symptomatic relief.⁷⁰ Contact lens wearers sensitized to pollen may be better served by switching to glasses during peak pollen seasons.⁶⁴ Contact lenses must be removed during the

administration of topical medications due to potential interaction between contact lenses and preservatives in ophthalmic medications but may be replaced after 10 minutes.^{71,72}

2. Medications:

Topical therapies for ocular allergy are outlined in **Table 5, 6 and 7**.⁷¹⁻⁸²

Artificial tears/Ocular lubricants

Refrigerated artificial tears may help mitigate co-morbid tear deficiency, wash away allergens and dilute inflammatory mediators on the ocular surface.⁷⁰ As patients use these frequently for symptomatic relief, single-dose preservative-free compounds are usually preferred to minimize toxic effects of preservatives.¹⁰ Ocular lubricants may be low, mid or high viscosity (**Table 5**). Low viscosity tears, usually prescribed for mild conditions, cause little interference with vision and offer great comfort. However, with a low residence time, the retention of benefits is less than higher viscosity tears, which, in turn, have greater blurring effects and are reserved for more severe cases.

Topical decongestants

Ocular decongestants reduce ocular erythema but have little effect on decreasing itching. Their long-term use may be limited by adverse effects such as ocular burning, mydriasis, worsening of narrow angle glaucoma, rebound hyperemia, conjunctivitis medicamentosa and tachyphylaxis.^{72,81} Caution should be exercised with ocular decongestants in patients with cardiovascular disease, hyperthyroidism and diabetes and they should be avoided altogether in patients with angle-closure glaucoma.^{71,83}

Antihistamines

Oral antihistamines are frequently used by patients often prior to seeking medical attention. However, the use and especially overuse of oral antihistamines, particularly first-generation antihistamines, may worsen dry eye syndrome, impair barrier protection of the tear film and, in some cases, worsen allergic conjunctivitis.^{10,70,82,84} The rapid onset of action and absence of systemic adverse effects, make topical antihistamines preferable to oral antihistamines. However, when topical antihistamines fail to provide adequate symptom control, adjunctive second-generation oral antihistamines may be considered as this combination is superior to monotherapy with oral antihistamines.^{10,85}

With their high efficacy and safety margin, topical antihistamines are often used as first line treatment for allergic conjunctivitis. They act as inverse agonists on the histamine receptor and block the acute phase allergic response.⁷¹ While they help relieve redness and itching, their short duration of action may necessitate more frequent dosing. The use of first-generation H1 antagonists, such as pheniramine, may be limited by ocular burning, short duration of action and limited potency.^{10,82} They are frequently combined with vasoconstrictors in over-the-counter formulations.¹⁰ Second generation antihistamines, such as emadastine, have a longer duration of action and better tolerability.^{10,85} A newer topical antihistamine, 0.24% cetirizine ophthalmic solution, showed good tolerability and efficacy in reducing both ocular and nasal signs and symptoms associated with allergic conjunctivitis.^{86,87} The use of topical antihistamines is contraindicated in patients at risk of acute angle closure glaucoma.⁷¹

Leukotriene Receptor Antagonists (LTRAs)

Montelukast blocks cysteinyl leukotriene receptor-1, and in one meta-analysis was more efficacious than placebo in treating seasonal allergic conjunctivitis in adult patients, but less

efficacious than oral antihistamines,⁸⁸ Of note, in March 2020 the U.S. Food and Drug Administration strengthened existing warnings about serious behavior and mood-related changes with montelukast and advised physicians to avoid prescribing montelukast for patients with mild symptoms.⁸⁹

Mast Cell (MC) Stabilizers

Mast cell stabilizers inhibit degranulation of MCs and prevent the release of mast cell mediators associated with the late phase of the allergic response. Most available single-action topical MC stabilizers (such as cromolyn, lodoxamide, nedocromil, pemirolast) require a preloading period, generally 3-5 days but up to 2 weeks, and frequent instillation, often leading to poor compliance.^{10,82} With the availability of newer agents that possess both antihistamine and MC stabilizing properties, the use of single-action MC stabilizers is usually limited to short-term add-on therapy.

Dual- or Multi-action agents

Many newer topical ophthalmic drugs work both as antihistamines and mast cell stabilizers. These often require less frequent instillation due to longer duration of action and have better tolerability than single-action antihistamines.^{71,90} Their antihistaminic effects provide rapid relief and their MC stabilizing effects afford more lasting benefit by inhibiting the late-phase response.^{71,85} Certain agents such as bepotastine have even been shown to alleviate rhinitis symptoms associated with allergic conjunctivitis.⁹¹ In contact lens wearers, epinastine increases comfortable wearing time and total wearing time, with decreased need for rewetting drops.⁹²

Topical NSAID (Non-steroidal anti-inflammatory drugs)

Ketorolac is the only FDA-approved ophthalmic NSAID available for treatment of SAC.^{10,93} It inhibits the downstream cascade of MC activation by blocking prostaglandin synthesis.^{10,93} With the availability of other ophthalmic preparations with better tolerability, the use of ketorolac is usually limited to intermittent use and as an add-on medication in patients with persistent symptoms while on other medications.

Topical Corticosteroids

Ocular corticosteroids modulate the MC response, thereby decreasing the recruitment of inflammatory cells and inhibiting cytokine production. The main pitfalls of therapy are cataract formation and intraocular pressure (IOP) increases.⁹⁴ Another risk of ocular corticosteroids is new or worsening viral or herpetic infections. Thus, ocular corticosteroids are reserved for symptoms that are severe or refractory to antihistamines. Dual acting agents, such as olapatadine, ketotifen and epinastine, have proven to be more efficacious than fluorometholone in preventing itching and hyperemia in patients with SAC.^{10,95}

Older ocular corticosteroids such as prednisolone, dexamethasone or fluorometholone may induce cataract formation. Newer formulations such as loteprednol, in which the ketone group at carbon-20 has been substituted with an ester group, have not been shown to increase the risk of cataracts, but may be associated with IOP increases at higher concentrations.^{71,94,96,97} To reduce this risk, ocular corticosteroids are prescribed for no more than 14 days. Patients on ocular corticosteroids for longer than 2 weeks should be monitored closely by an ophthalmologist for the development of any adverse effects. Patients with lid eczema, sometimes arising from local contact dermatitis, may benefit from local application of 1% hydrocortisone cream.¹⁰ Generally, the use of higher potency topical corticosteroids is avoided in the peri-orbital area.

Several studies have demonstrated a beneficial effect of intranasal corticosteroids (INS) on ocular symptoms, presumably via the ocular-nasal reflex inhibition.^{63,74} INS effectively reduce TOSS and are well-tolerated in ARC.^{74,98} There has long been a concern that prolonged use of INS might increase the development of glaucoma or the development of cataracts. While a statistically significant increase in intraocular pressure compared with placebo has been detected, the levels usually remain within normal range and glaucomatous optic disc changes have not been noted⁹⁹. A recent systematic review and meta-analysis looked at over 424 studies, including 10 randomized controlled trials to help answer these questions¹⁰⁰. The authors found that the absolute increased incidence of elevated IOP in patients using INCS vs. placebo was 0.8% but there were no cases of glaucoma at 12 months¹⁰⁰. The absolute increased risk of developing a posterior cataract was 0.02%¹⁰⁰. INS, such as fluticasone or mometasone, have little to no systemic absorption and have not been shown to increase the risk of cataracts or glaucoma.⁷⁴ Systemic corticosteroids are reserved as short courses for severe exacerbations with eyelid dermatitis or corneal involvement in AKC or VKC.⁷⁴ When using intranasal corticosteroids on a prolonged basis, especially in high doses, an annual eye exam and IOP measurement should be considered⁹⁹.

Calcineurin inhibitors

Topical calcineurin inhibitors such as cyclosporine or tacrolimus may be considered in severe or refractory allergic conjunctivitis, VKC and AKC, especially in preventing seasonal recurrences and for steroid-sparing effects.¹⁰¹ A cyclosporine ophthalmic emulsion (0.05%) is FDA-approved for the treatment of dry eye syndrome. Application of topical tacrolimus 0.1% or 0.03% ointment and 1% pimecrolimus cream is effective in treating VKC, AKC and eyelid atopic dermatitis, but pose a risk of local infections such as molluscum contagiosum, papilloma

virus and herpes.^{70,74,102-104} Compliance may also be limited by burning sensation. Systemic cyclosporine may be considered in vision threatening refractory AKC.^{105,106}

Immunomodulating drugs

Use of systemic immunomodulating drugs such as methotrexate, azathioprine or mycophenolate mophetil is limited to serious inflammatory ocular disease such as uveitis or scleritis, and their use is seldom, if ever, warranted for ocular allergy.¹⁰⁷

3. Allergen Immunotherapy:

In 1911, Noon et al. demonstrated the efficacy of prophylactic immunotherapy in preventing ocular symptoms precipitated by conjunctival allergen challenges.¹⁰⁸ Allergen immunotherapy is reserved for patients with IgE sensitization to relevant aeroallergens. It may be a good option for patients with inadequate symptom control despite pharmacotherapy and allergen avoidance or those who cannot tolerate medications or find long-term compliance difficult. There are currently two modalities for allergen immunotherapy in the United States – subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Most studies relating to the efficacy of allergen immunotherapy have been conducted in patients with allergic rhinoconjunctivitis rather than allergic conjunctivitis alone. Allergen immunotherapy increases the allergen sensitivity threshold and helps decrease ocular symptoms and medication use.^{10,109,110} In a prospective comparative case series study of patients with IgE-mediated allergic conjunctivitis receiving either SLIT or SCIT, both groups had meaningful clinical and immunological improvement as evidenced by improved TOSS, decreased medication use, decreased total IgE level and SPT wheal diameter 1 year after treatment, without significant difference between the two routes of immunotherapy.¹¹¹

4. Interventional Procedures:

In intractable cases of ocular allergy, especially VKC, supra-tarsal conjunctival injection of triamcinolone acetonide or betamethasone suspension has been suggested.^{24,112-114} Tarsal conjunctival resection may be performed in patients with progressive conjunctival papillary hyperplasia; however, recurrence is common.⁶⁴ Patients with chronic ocular allergy may develop punctal stenosis either secondary to uncontrolled conjunctival inflammation or due to membrane formation over the punctum from chronic use of topical medications.^{2,115,116} In patients with PAC with relapsing symptoms and punctal stenosis, mini-monoka stenting and bicanalicular silicone intubation are well-tolerated and effective interventions to treat acquired punctal stenosis from allergic conjunctivitis.^{2,115-117} Chronic severe VKC and AKC may lead to conjunctival epithelial ingrowth on the cornea, recurrent corneal epithelial defects and neovascularization, a condition known as limbal stem cell deficiency (LSCD).⁷⁴ A recent study showed that surgical rehabilitation with procedures such as limbal stem cell transplantation, Boston keratoprosthesis and superficial keratectomy in patients with advanced ocular surface disease arising from chronic severe AKC has mixed outcomes, with some cases developing visual loss. Thus early medical intervention with immunomodulators is warranted to prevent the development of LSCD.¹¹⁸

5. Emerging Therapies:

Recently, a large-scale assessment testing a contact lens based drug delivery system for therapeutic delivery of ketotifen proved to be comparable to direct topical drug delivery, thereby providing a mechanism for simultaneous vision correction and anti-allergic treatment for contact lens wearers with ocular allergy.¹¹⁹ Also, epinastine hydrochloride releasing soft contact lenses demonstrated prolonged drug release and significantly greater efficacy over the use of epinastine hydrochloride eye drops 12 hours after treatment.¹²⁰

Omalizumab, a recombinant anti-IgE monoclonal antibody, has shown decreased burning, itching and need for topical antihistamines, topical and oral steroids, improvement in lid eczema and improved quality of life in case reports and series of patients with severe VKC and AKC, despite failure of immunosuppressive therapies.¹²¹⁻¹²⁷ Patients may have relapse of symptoms on discontinuation of omalizumab, but symptoms remit upon drug re-initiation.¹²⁴ Efficacy may be incomplete or limited in severe cases.¹²⁷

- **Follow up and monitoring:**

It is important to arrange for periodic follow up of patients with allergic ocular conditions, especially in seasons of peak symptoms. Visual acuity measurement and SLE is advised for all ocular allergy patients at follow-up visits. Patients using intra-ocular steroids should be monitored for the development of glaucoma and cataracts⁹⁹. As discussed earlier, while the risk of developing glaucoma and/or cataracts from the use of INS is extremely unlikely, patients with prolonged use of INS should be encouraged to have an annual eye exam to monitor for these potential adverse events⁹⁹. Allergic ocular diseases, especially AKC, can be complicated by the development of keratoconus and corneal ectasia, staphylococcal blepharitis, herpes simplex superinfection, corneal plaques and ulceration and co-management with an ophthalmologist may be needed.^{21,70}

- **Conclusion:**

Our understanding of ocular allergy has significantly advanced since its first description 200 years ago. However, there remain many unmet needs. Screening and follow-up questionnaires in ocular allergy require standardization.⁵⁷ There also needs to be standardization of tests such as measurement of tear IgE or tear inflammatory mediators and evaluating naso-ocular symptoms in

486 response to CPT.⁵⁷ In recent years, research in biological medications has focused more
487 extensively on other allergic diseases such as asthma, atopic dermatitis and nasal polyps. While
488 some of these agents have shown efficacy in patients with concomitant allergic conjunctivitis,
489 studies investigating their value in treating isolated ocular allergy are lacking, especially more
490 severe forms such as VKC or AKC. Clinical and research advances can be made by greater
491 collaboration between the allergist and the eye-care specialist.

Acknowledgements: Collaborators: This scientific review was initiated in 2018 as a project of the ACAAI Rhinitis/Sinusitis/Ocular committee. The authors are current and/or past members of this scientific committee. Prior to submission for publication to *Annals of Allergy, Asthma, and Immunology*, the manuscript was also reviewed by the following committee members: John Hagan, Punita Ponda and Anjeni Keswani. We would like to thank Kathleen Rowland-Hong for assistance with illustration A in Figure 1 and Dr. Jacob Lang, OD, for contributing photos B-E towards Figure 1 in this publication.

1. Bostock J. Case of a Periodical Affection of the Eyes and Chest. *Med Chir Trans*. 1819;10(Pt 1):161-165.
2. Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol*. 2015;15(5):482-488.
3. Petricek I, Prost M, Popova A. The differential diagnosis of red eye: a survey of medical practitioners from Eastern Europe and the Middle East. *Ophthalmologica*. 2006;220(4):229-237.
4. Williams DC, Edney G, Maiden B, Smith PK. Recognition of allergic conjunctivitis in patients with allergic rhinitis. *World Allergy Organ J*. 2013;6(1):4.
5. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. *J Allergy Clin Immunol*. 2010;126(4):778-783 e776.
6. Meng Q, Nagarajan S, Son Y, Koutsoupias P, Bielory L. Asthma, oculonasal symptoms, and skin test sensitivity across National Health and Nutrition Examination Surveys. *Ann Allergy Asthma Immunol*. 2016;116(2):118-125 e115.
7. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. *J Allergy Clin Immunol*. 2005;115(1):118-122.
8. Bielory L, Skoner DP, Blaiss MS, et al. Ocular and nasal allergy symptom burden in America: the Allergies, Immunotherapy, and Rhinoconjunctivitis (AIRS) surveys. *Allergy Asthma Proc*. 2014;35(3):211-218.
9. Cibella F, Ferrante G, Cuttitta G, et al. The burden of rhinitis and rhinoconjunctivitis in adolescents. *Allergy Asthma Immunol Res*. 2015;7(1):44-50.
10. Leonardi A, Bogacka E, Fauquert JL, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy*. 2012;67(11):1327-1337.
11. Vichyanond P, Pacharn P, Pleyer U, Leonardi A. Vernal keratoconjunctivitis: a severe allergic eye disease with remodeling changes. *Pediatr Allergy Immunol*. 2014;25(4):314-322.
12. Passali D, Cingi C, Staffa P, Passali F, Muluk NB, Bellussi ML. The International Study of the Allergic Rhinitis Survey: outcomes from 4 geographical regions. *Asia Pac Allergy*. 2018;8(1):e7.
13. Addis H, Jeng BH. Vernal keratoconjunctivitis. *Clin Ophthalmol*. 2018;12:119-123.
14. Zicari AM, Capata G, Nebbioso M, et al. Vernal Keratoconjunctivitis: an update focused on clinical grading system. *Ital J Pediatr*. 2019;45(1):64.
15. Bremond-Gignac D, Donadieu J, Leonardi A, et al. Prevalence of vernal keratoconjunctivitis: a rare disease? *Br J Ophthalmol*. 2008;92(8):1097-1102.
16. Chen JJ, Applebaum DS, Sun GS, Pflugfelder SC. Atopic keratoconjunctivitis: A review. *J Am Acad Dermatol*. 2014;70(3):569-575.
17. Moscovici BK, Cesar AS, Nishiwaki-Dantas MC, Mayor SA, Marta AC, Marques JC. [Atopic keratoconjunctivitis in patients of the pediatric dermatology ambulatory in a reference center]. *Arq Bras Oftalmol*. 2009;72(6):805-810.
18. Bielory B, Bielory L. Atopic dermatitis and keratoconjunctivitis. *Immunol Allergy Clin North Am*. 2010;30(3):323-336.
19. Tuft SJ, Kemeny DM, Dart JK, Buckley RJ. Clinical features of atopic keratoconjunctivitis. *Ophthalmology*. 1991;98(2):150-158.

20. Guglielmetti S, Dart JK, Calder V. Atopic keratoconjunctivitis and atopic dermatitis. *Curr Opin Allergy Clin Immunol*. 2010;10(5):478-485.
21. Patel N, Venkateswaran N, Wang Z, Galor A. Ocular involvement in atopic disease: a review. *Curr Opin Ophthalmol*. 2018;29(6):576-581.
22. Kari O, Saari KM. Diagnostics and new developments in the treatment of ocular allergies. *Curr Allergy Asthma Rep*. 2012;12(3):232-239.
23. Peiser M, Tralau T, Heidler J, et al. Allergic contact dermatitis: epidemiology, molecular mechanisms, in vitro methods and regulatory aspects. Current knowledge assembled at an international workshop at BfR, Germany. *Cell Mol Life Sci*. 2012;69(5):763-781.
24. Rietschel RL, Warshaw EM, Sasseville D, et al. Common contact allergens associated with eyelid dermatitis: data from the North American Contact Dermatitis Group 2003-2004 study period. *Dermatitis*. 2007;18(2):78-81.
25. Fukuda K, Ohbayashi M, Morohoshi K, Zhang L, Liu FT, Ono SJ. Critical role of IgE-dependent mast cell activation in a murine model of allergic conjunctivitis. *J Allergy Clin Immunol*. 2009;124(4):827-833 e822.
26. Hoffmann-Sommergruber K, Ferreira ED, Ebner C, et al. Detection of allergen-specific IgE in tears of grass pollen-allergic patients with allergic rhinoconjunctivitis. *Clin Exp Allergy*. 1996;26(1):79-87.
27. Saban DR. The chemokine receptor CCR7 expressed by dendritic cells: a key player in corneal and ocular surface inflammation. *Ocul Surf*. 2014;12(2):87-99.
28. Leonardi A. Allergy and allergic mediators in tears. *Exp Eye Res*. 2013;117:106-117.
29. Pelikan Z. Mediator profiles in tears during the conjunctival response induced by allergic reaction in the nasal mucosa. *Mol Vis*. 2013;19:1453-1470.
30. Zicari AM, Nebbioso M, Zicari A, et al. Serum levels of IL-17 in patients with vernal keratoconjunctivitis: a preliminary report. *Eur Rev Med Pharmacol Sci*. 2013;17(9):1242-1244.
31. Yokoi K, Yokoi N, Kinoshita S. Impairment of ocular surface epithelium barrier function in patients with atopic dermatitis. *Br J Ophthalmol*. 1998;82(7):797-800.
32. Garcia-Posadas L, Hodges RR, Diebold Y, Dartt DA. Context-Dependent Regulation of Conjunctival Goblet Cell Function by Allergic Mediators. *Sci Rep*. 2018;8(1):12162.
33. Dogru M, Matsumoto Y, Okada N, et al. Alterations of the ocular surface epithelial MUC16 and goblet cell MUC5AC in patients with atopic keratoconjunctivitis. *Allergy*. 2008;63(10):1324-1334.
34. Fujishima H, Okada N, Matsumoto K, et al. The usefulness of measuring tear periostin for the diagnosis and management of ocular allergic diseases. *J Allergy Clin Immunol*. 2016;138(2):459-467 e452.
35. Leonardi A, De Dominicis C, Motterle L. Immunopathogenesis of ocular allergy: a schematic approach to different clinical entities. *Curr Opin Allergy Clin Immunol*. 2007;7(5):429-435.
36. Hom MM, Nguyen AL, Bielory L. Allergic conjunctivitis and dry eye syndrome. *Ann Allergy Asthma Immunol*. 2012;108(3):163-166.
37. Hom M, Nguyen A, Bielory L.
38. Ward KW. Superficial punctate fluorescein staining of the ocular surface. *Optom Vis Sci*. 2008;85(1):8-16.
39. Hom MM, O'Dell L, Bielory L. Ocular papillary changes on the caruncle surgace in allergic conjunctivitis. *J Allergy Clin Immunol*. 2015;135(2):AB272.

40. Begley CG, Riggall A, Tuel JA. Association of giant papillary conjunctivitis with seasonal allergies. *Optom Vis Sci.* 1990;67(3):192-195.
41. Farrand KF, Fridman M, Stillman IO, Schaumberg DA. Prevalence of Diagnosed Dry Eye Disease in the United States Among Adults Aged 18 Years and Older. *Am J Ophthalmol.* 2017;182:90-98.
42. 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):75-92.
43. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf.* 2017;15(3):276-283.
44. Jabs DA, Mudun A, Dunn JP, Marsh MJ. Episcleritis and scleritis: clinical features and treatment results. *Am J Ophthalmol.* 2000;130(4):469-476.
45. Baudouin C, Pisella PJ, Fillacier K, et al. Ocular surface inflammatory changes induced by topical antiglaucoma drugs: human and animal studies. *Ophthalmology.* 1999;106(3):556-563.
46. Hong J, Bielory L. Allergy to ophthalmic preservatives. *Curr Opin Allergy Clin Immunol.* 2009;9(5):447-453.
47. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10086):2287-2303.
48. de Bruin-Weller M, Thaci D, Smith CH, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). *Br J Dermatol.* 2018;178(5):1083-1101.
49. Simpson EL, Akinlade B, Ardeleanu M. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med.* 2017;376(11):1090-1091.
50. Wollenberg A, Ariens L, Thurau S, van Luijk C, Seegraber M, de Bruin-Weller M. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab-clinical characteristics and treatment. *J Allergy Clin Immunol Pract.* 2018;6(5):1778-1780 e1771.
51. Treister AD, Kraff-Cooper C, Lio PA. Learning About Dupilumab-Associated Conjunctivitis-Reply. *JAMA Dermatol.* 2019;155(6):754-755.
52. Thyssen JP, de Bruin-Weller MS, Paller AS, et al. Conjunctivitis in atopic dermatitis patients with and without dupilumab therapy - international eczema council survey and opinion. *J Eur Acad Dermatol Venereol.* 2019;33(7):1224-1231.
53. Bakker DS, Ariens LFM, van Luijk C, et al. Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis. *Br J Dermatol.* 2019;180(5):1248-1249.
54. Agnihotri G, Shi K, Lio PA. A Clinician's Guide to the Recognition and Management of Dupilumab-Associated Conjunctivitis. *Drugs R D.* 2019;19(4):311-318.
55. Maudinet A, Law-Koune S, Duretz C, Lasek A, Modiano P, Tran THC. Ocular Surface Diseases Induced by Dupilumab in Severe Atopic Dermatitis. *Ophthalmol Ther.* 2019;8(3):485-490.

56. Aszodi N, Thureau S, Seegraber M, de Bruin-Weller M, Wollenberg A. Management of dupilumab-associated conjunctivitis in atopic dermatitis. *J Dtsch Dermatol Ges*. 2019;17(5):488-491.
57. Leonardi A, Doan S, Fauquert JL, et al. Diagnostic tools in ocular allergy. *Allergy*. 2017;72(10):1485-1498.
58. Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in Rhinology EAACI position paper. *Clin Transl Allergy*. 2011;1(1):2.
59. Leonardi A, Borghesan F, Scalora T, Modugno RL, Bonaldo A. Office-based ocular procedures for the allergist. *Curr Opin Allergy Clin Immunol*. 2019;19(5):488-494.
60. Mimura T, Usui T, Yamagami S, Miyai T, Amano S. Relation between total tear IgE and severity of acute seasonal allergic conjunctivitis. *Curr Eye Res*. 2012;37(10):864-870.
61. Nomura K, Takamura E. Tear IgE concentrations in allergic conjunctivitis. *Eye (Lond)*. 1998;12 (Pt 2):296-298.
62. Fauquert JL, Jedrzejczak-Czechowicz M, Rondon C, et al. Conjunctival allergen provocation test : guidelines for daily practice. *Allergy*. 2017;72(1):43-54.
63. Adkinson NF, Bochner BS, Burks AW, et al. *Middleton's Allergy: Principles and Practice: Eighth Edition*. Elsevier Inc.; 2013.
64. Takamura E, Uchio E, Ebihara N, et al. Japanese guidelines for allergic conjunctival diseases 2017. *Allergol Int*. 2017;66(2):220-229.
65. Leonardi A, Battista MC, Gismondi M, Fregona IA, Secchi AG. Antigen sensitivity evaluated by tear-specific and serum-specific IgE, skin tests, and conjunctival and nasal provocation tests in patients with ocular allergic disease. *Eye (Lond)*. 1993;7 (Pt 3):461-464.
66. Bielory L. Ocular symptom reduction in patients with seasonal allergic rhinitis treated with the intranasal corticosteroid mometasone furoate. *Ann Allergy Asthma Immunol*. 2008;100(3):272-279.
67. Bielory L, Hom MM, Nguyen AL. Relationship between TOSS questionnaire and two dry eye questionnaires (OSDI and SEsoD). *Invest Ophthalmol Vis Sci*. 2012;53(4):537.
68. Sacchetti M, Baiardini I, Lambiase A, et al. Development and testing of the quality of life in children with vernal keratoconjunctivitis questionnaire. *Am J Ophthalmol*. 2007;144(4):557-563.
69. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5 Suppl):S147-334.
70. Varu DM, Rhee MK, Akpek EK, et al. Conjunctivitis Preferred Practice Pattern(R). *Ophthalmology*. 2019;126(1):P94-P169.
71. Bielory L, Meltzer EO, Nichols KK, Melton R, Thomas RK, Bartlett JD. An algorithm for the management of allergic conjunctivitis. *Allergy Asthma Proc*. 2013;34(5):408-420.
72. Bielory L, Schoenberg D. Emerging Therapeutics for Ocular Surface Disease. *Curr Allergy Asthma Rep*. 2019;19(3):16.
73. Bielory L, Wagle P. Ocular surface lubricants. *Curr Opin Allergy Clin Immunol*. 2017;17(5):382-389.
74. Leonardi A, Silva D, Perez Formigo D, et al. Management of ocular allergy. *Allergy*. 2019;74(9):1611-1630.
75. Berger WE, Granet DB, Kabat AG. Diagnosis and management of allergic conjunctivitis in pediatric patients. *Allergy Asthma Proc*. 2017;38(1):16-27.

76. Ben-Eli H, Solomon A. Topical antihistamines, mast cell stabilizers, and dual-action agents in ocular allergy: current trends. *Curr Opin Allergy Clin Immunol*. 2018;18(5):411-416.
77. Carr W, Schaeffer J, Donnenfeld E. Treating allergic conjunctivitis: A once-daily medication that provides 24-hour symptom relief. *Allergy Rhinol (Providence)*. 2016;7(2):107-114.
78. Woerly G, Loiseau S, Loyens M, Schoch C, Capron M. Inhibitory effects of ketotifen on eotaxin-dependent activation of eosinophils: consequences for allergic eye diseases. *Allergy*. 2003;58(5):397-406.
79. Nabe M, Miyagawa H, Agrawal DK, Sugiyama H, Townley RG. The effect of ketotifen on eosinophils as measured at LTC₄ release and by chemotaxis. *Allergy Proc*. 1991;12(4):267-271.
80. Canonica GW, Ciprandi G, Petzold U, Kolb C, Ellers-Lenz B, Hermann R. Topical azelastine in perennial allergic conjunctivitis. *Curr Med Res Opin*. 2003;19(4):321-329.
81. La Rosa M, Lionetti E, Reibaldi M, et al. Allergic conjunctivitis: a comprehensive review of the literature. *Ital J Pediatr*. 2013;39:18.
82. Bielory L, Lien KW, Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. *Drugs*. 2005;65(2):215-228.
83. Fraunfelder FT, Meyer SM. Systemic reactions to ophthalmic drug preparations. *Med Toxicol Adverse Drug Exp*. 1987;2(4):287-293.
84. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466-476.
85. Abelson MB, McLaughlin JT, Gomes PJ. Antihistamines in ocular allergy: are they all created equal? *Curr Allergy Asthma Rep*. 2011;11(3):205-211.
86. Meier EJ, Torkildsen GL, Gomes PJ, Jasek MC. Phase III trials examining the efficacy of cetirizine ophthalmic solution 0.24% compared to vehicle for the treatment of allergic conjunctivitis in the conjunctival allergen challenge model. *Clin Ophthalmol*. 2018;12:2617-2628.
87. Malhotra RP, Meier E, Torkildsen G, Gomes PJ, Jasek MC. Safety of cetirizine ophthalmic solution 0.24% for the treatment of allergic conjunctivitis in adult and pediatric subjects. *Clin Ophthalmol*. 2019;13:403-413.
88. Gane J, Buckley R. Leukotriene receptor antagonists in allergic eye disease: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract*. 2013;1(1):65-74.
89. Administration USFaD. FDA requires boxed warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. FDA. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug>. Published 2020. Updated 03/13/2020. Accessed 04/07/2020, 2020.
90. Wade L, Bielory L, Rudner S. Ophthalmic antihistamines and H1-H4 receptors. *Curr Opin Allergy Clin Immunol*. 2012;12(5):510-516.
91. Cavet ME, Gomes PJ, Carr WW, Williams JI. Bepotastine besilate ophthalmic solution 1.5% for alleviating nasal symptoms in patients with allergic conjunctivitis. *J Asthma Allergy*. 2018;11:29-39.

92. Nichols KK, Morris S, Gaddie IB, Evans D. Epinastine 0.05% ophthalmic solution in contact lens-wearing subjects with a history of allergic conjunctivitis. *Eye Contact Lens*. 2009;35(1):26-31.
93. Ballas Z, Blumenthal M, Tinkelman DG, Kriz R, Rupp G. Clinical evaluation of ketorolac tromethamine 0.5% ophthalmic solution for the treatment of seasonal allergic conjunctivitis. *Surv Ophthalmol*. 1993;38 Suppl:141-148.
94. Ilyas H, Slonim CB, Braswell GR, Favetta JR, Schulman M. Long-term safety of loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis. *Eye Contact Lens*. 2004;30(1):10-13.
95. Borazan M, Karalezli A, Akova YA, Akman A, Kiyici H, Erbek SS. Efficacy of olopatadine HCl 0.1%, ketotifen fumarate 0.025%, epinastine HCl 0.05%, emedastine 0.05% and fluorometholone acetate 0.1% ophthalmic solutions for seasonal allergic conjunctivitis: a placebo-controlled environmental trial. *Acta Ophthalmol*. 2009;87(5):549-554.
96. Bielory BP, Perez VL, Bielory L. Treatment of seasonal allergic conjunctivitis with ophthalmic corticosteroids: in search of the perfect ocular corticosteroids in the treatment of allergic conjunctivitis. *Curr Opin Allergy Clin Immunol*. 2010;10(5):469-477.
97. Wu LQ, Chen X, Lou H, Cheng JW, Wei RL. Loteprednol etabonate in the treatment of allergic conjunctivitis: a meta-analysis. *Curr Med Res Opin*. 2015;31(8):1509-1518.
98. Hong J, Bielory B, Rosenberg JL, Bielory L. Efficacy of intranasal corticosteroids for the ocular symptoms of allergic rhinitis: A systematic review. *Allergy Asthma Proc*. 2011;32(1):22-35.
99. Mohd Zain A, Md Noh UK, Hussein S, Che Hamzah J, Mohd Khialdin S, Md Din N. The Relationship Between Long-term Use of Intranasal Corticosteroid and Intraocular Pressure. *J Glaucoma*. 2019;28(4):321-324.
100. Valenzuela CV, Liu JC, Vila PM, Simon L, Doering M, Lieu JEC. Intranasal Corticosteroids Do Not Lead to Ocular Changes: A Systematic Review and Meta-analysis. *Laryngoscope*. 2019;129(1):6-12.
101. Lambiase A, Leonardi A, Sacchetti M, Deligianni V, Sposato S, Bonini S. Topical cyclosporine prevents seasonal recurrences of vernal keratoconjunctivitis in a randomized, double-masked, controlled 2-year study. *J Allergy Clin Immunol*. 2011;128(4):896-897 e899.
102. Vichyanond P, Tantimongkolsuk C, Dumrongkigchaiporn P, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P. Vernal keratoconjunctivitis: Result of a novel therapy with 0.1% topical ophthalmic FK-506 ointment. *J Allergy Clin Immunol*. 2004;113(2):355-358.
103. Attas-Fox L, Barkana Y, Iskhakov V, et al. Topical tacrolimus 0.03% ointment for intractable allergic conjunctivitis: an open-label pilot study. *Curr Eye Res*. 2008;33(7):545-549.
104. Chen SL, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials. *J Dermatolog Treat*. 2010;21(3):144-156.
105. Cornish KS, Gregory ME, Ramaesh K. Systemic cyclosporin A in severe atopic keratoconjunctivitis. *Eur J Ophthalmol*. 2010;20(5):844-851.
106. Hoang-Xuan T, Prisant O, Hannouche D, Robin H. Systemic cyclosporine A in severe atopic keratoconjunctivitis. *Ophthalmology*. 1997;104(8):1300-1305.

107. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. *Ophthalmology*. 2008;115(10):1826-1832.
108. Noon L, Cantab BC. Prophylactic inoculation against hay fever. *Lancet*. 2011;1:1572-1574.
109. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. *Cochrane Database Syst Rev*. 2011(7):CD007685.
110. Frolund L, Durham SR, Calderon M, et al. Sustained effect of SQ-standardized grass allergy immunotherapy tablet on rhinoconjunctivitis quality of life. *Allergy*. 2010;65(6):753-757.
111. Sayed KM, Kamel AG, Ali AH. One-year evaluation of clinical and immunological efficacy and safety of sublingual versus subcutaneous allergen immunotherapy in allergic conjunctivitis. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(9):1989-1996.
112. Costa AXD, Gomes JAP, Marculino LGC, Liendo VL, Barreiro TP, Santos MSD. Supratarsal injection of triamcinolone for severe vernal keratoconjunctivitis in children. *Arq Bras Oftalmol*. 2017;80(3):186-188.
113. Singh S, Pal V, Dhull CS. Supratarsal injection of corticosteroids in the treatment of refractory vernal keratoconjunctivitis. *Indian J Ophthalmol*. 2001;49(4):241-245.
114. Holsclaw DS, Whitcher JP, Wong IG, Margolis TP. Supratarsal injection of corticosteroid in the treatment of refractory vernal keratoconjunctivitis. *Am J Ophthalmol*. 1996;121(3):243-249.
115. Alsulaiman N, Alsuhaibani AH. Bicanalicular Silicone Intubation for the Management of Punctal Stenosis and Obstruction in Patients With Allergic Conjunctivitis. *Ophthalmic Plast Reconstr Surg*. 2019;35(5):451-455.
116. McNab AA. Lacrimal canalicular obstruction associated with topical ocular medication. *Aust N Z J Ophthalmol*. 1998;26(3):219-223.
117. Or L, Zadok D, Hartstein ME. Mini-monoka stenting for patients with perennial allergic conjunctivitis. *Orbit*. 2019;38(4):285-289.
118. Jabbehdari S, Starnes TW, Kurji KH, et al. Management of advanced ocular surface disease in patients with severe atopic keratoconjunctivitis. *Ocul Surf*. 2019;17(2):303-309.
119. Pall B, Gomes P, Yi F, Torkildsen G. Management of Ocular Allergy Itch With an Antihistamine-Releasing Contact Lens. *Cornea*. 2019;38(6):713-717.
120. Minami T, Ishida W, Kishimoto T, et al. In vitro and in vivo performance of epinastine hydrochloride-releasing contact lenses. *PLoS One*. 2019;14(1):e0210362.
121. de Klerk TA, Sharma V, Arkwright PD, Biswas S. Severe vernal keratoconjunctivitis successfully treated with subcutaneous omalizumab. *J AAPOS*. 2013;17(3):305-306.
122. Taille C, Doan S, Neukirch C, Aubier M. Omalizumab for severe atopic keratoconjunctivitis. *BMJ Case Rep*. 2010;2010.
123. Simpson RS, Lee JK. Omalizumab as single-dose therapy for vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol*. 2019;122(1):119-120.
124. Santamaria L, Sanchez J. [Long-term efficacy of omalizumab in patients with conventional treatment-resistant vernal keratoconjunctivitis]. *Rev Alerg Mex*. 2018;65(2):192-196.

125. Occasi F, Duse M, Nebbioso M, et al. Vernal keratoconjunctivitis treated with omalizumab: A case series. *Pediatr Allergy Immunol.* 2017;28(5):503-505.
126. Heffler E, Picardi G, Liuzzo MT, Pistorio MP, Crimi N. Omalizumab Treatment of Vernal Keratoconjunctivitis. *JAMA Ophthalmol.* 2016;134(4):461-463.
127. Doan S, Amat F, Gabison E, Saf S, Cochereau I, Just J. Omalizumab in Severe Refractory Vernal Keratoconjunctivitis in Children: Case Series and Review of the Literature. *Ophthalmol Ther.* 2017;6(1):195-206.

	SAC	PAC	VKC	AKC	CBC
Pattern/frequency	Intermittent, usually Spring	Persistent	Persistent, worse in spring, summer	Persistent with exacerbations	Intermittent/persistent
Co-morbid conditions	Allergic rhinitis, allergic asthma	Allergic rhinitis, allergic asthma	Allergic rhinitis, SAC>PAC	Atopic dermatitis, asthma, allergic rhinitis	Contact dermatitis of other skin sites, remote from eyes
Age/sex	Onset Childhood & young adult	Onset Childhood & young adult	Childhood, ends by age 20; M>F	Usually adult age 30-50, can start childhood	Middle-aged or older; F:M= 2:1.
Trigger	Pollen	Dust mite, animal dander, other perennial allergens	Grass/tree pollen, hot & humid environment	Spring & summer seasonal/perennial allergens may worsen	Low molecular weight chemicals, e.g., cosmetics/medications near eye
Pathophysiology	IgE, atopy, AR usually present	IgE, atopy, AR usually present	IgE/non-IgE, atopy, often AR	IgE & cell-mediated, co-morbid atopic dermatitis (95%) & asthma (87%), eosinophils +	Non-IgE, Type IV, lymphocyte mediated
Conjunctival findings	Injection, bulbar & palpebral hyperemia, chemosis, clear watery discharge, follicles, papillae	Injection, bulbar & palpebral hyperemia , chemosis, clear watery discharge; follicles, papillae	Cobblestoning & giant papillae upper tarsal conjunctiva; scarring uncommon; stringy mucoïd discharge; hyperemia; many eosinophils	Cobblestoning & giant papillae in inferior fornix, hyperemia, lower > upper bulbar palpebral involvement, chemosis, scarring, watery or mucoïd discharge; eosinophils present	Conjunctival involvement has been reported

Cornea	No change	No change	Superficial Punctate Keratitis, shield ulcer, plaque, revascularization; scarring uncommon	Neovascularization; cicatrization, keratopathy. scarring; keratoconus (rare), anterior subcapsular cataracts	N/A
Eyelids	Edema +/-	Edema +/-	Edema	Thickened, lichenified, scarring, ectropion, entropion, madarosis, irregular margins, eczema with sandpaper texture, hyperpigmentation, ptosis, anterior & posterior blepharitis	Usually involved with contact dermatitis with scaling, crusting
Limbus	N/A	N/A	++ Trantas dots superior limbus, +/- thickening	+ Trantas dots	N/A
Pruritus	++ to +++	++	+++	++	++
Other symptoms	Burning	Burning		Periorbital eczema	Periorbital eczema
Photophobia	+ Mild if present	+ Mild if present	++	++	Usually not present
Eye pain	No	No	++ with corneal involvement	++ with corneal involvement	No
Visual involvement	+, blurring	+, blurring	++ with corneal involvement	++ with corneal involvement, visual loss rare	No

Table 1: Classification and Clinical Features of Ocular Allergic Diseases

Legend: AKC, atopic keratoconjunctivitis; CBC, contact blepharoconjunctivitis; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; VKC, vernal keratoconjunctivitis. +/- = may be present or absent; += mild; ++= moderate; +++= severe.

	GPC	DED	IFC	K	S	ES	IS	DITC
Pattern/ Frequency	Persistent	Persistent	Acute episodic	Acute onset	Acute onset	Acute onset, lasting 3 wks., often recurrent	Acute or insidious	Onset after prolonged use of ocular meds, especially in glaucoma patients
Age most common	Adolescents and young adults; atopic population	> age 50 y, F>M	Children> adults	Any age	Adults, onset 47-60 y, F>M	~45 y, 70% F	Adult>child	Adults

Trigger	Soft CL, CL solution, ocular prosthesis and/or sutures; SAC may be a risk factor for exacerbation	↓ androgens; drying systemic meds, ocular meds, CL, windy/low humidity areas, systemic diseases	Bacterial or viral infection	Bacterial infection due to CL contamination; viral infection, e.g., herpes	Autoimmune diseases (50%), infectious, malignancy, post-surgical, medication side effects, idiopathic	Idiopathic, DED, or underlying systemic disease, e.g., rheumatoid arthritis	Immune-mediated or infectious systemic disease	Ocular drugs & preservatives and systemic drugs
Pathophysiology	Irritant, e.g. repetitive mechanical; elevated eosinophils, mast cells, basophils conjunctiva, increased IgE in tears	Reduced production and increased evaporation of tears	Infection of conjunctiva	Infection of cornea	Exact pathophysiology unknown histopathological features of vasculitic conditions	Type I, III, or IV hypersensitivity reaction	Infectious or systemic immune-mediated disease	Type IV hypersensitivity reaction to drugs/preservatives
Pruritus	+ to ++		0-+1	None	None	None	None	+ to ++

Photophobia	+	None	+	+++	++	Rare	+ to +++	+
Eye pain	+/-	+/-	+ to ++	+++	+++, boring	+/-	+ to +++	rare
Visual involvement	Blurred vision	Blurred vision that may clear with blinking	Blurred	Potential vision loss	Blurred vision, potential vision loss	None	Constricted pupil; visual loss can occur	Potential visual loss, systemic>topical medications
Other symptoms	Grittiness/foreign body sensation +, mucoid discharge	Grittiness, irritation, reduced blink rate, grittiness	Viral conjunctivitis: grittiness, burning, URI, fever, systemic symptoms , and enlarged & tender pre-auricular lymph nodes	Foreign body sensation +++	Headache, tenderness over eye	Irritation, watery discharge	No foreign body sensation, ciliary flush most always present	Burning ++, foreign body sensation

Table 2: Differential diagnosis of ocular allergy – demographics and symptomatology

Legend: CL, contact lens; DED, dry eye disease; DITC, drug-induced toxic conjunctivitis; ES, episcleritis; GPC, giant papillary conjunctivitis; IS, Iritis; IFC, infectious conjunctivitis; K, keratitis; S, scleritis; SAC, seasonal allergic conjunctivitis; URI, upper respiratory infection. +/- = may be present or absent; += mild; ++= moderate; +++= severe.

	GPC	DED	IFC	K	S	ES	IS	DITC
Conjunctival [Scleral/Episcleral] findings	Cobblestoning & giant papillae or medium/small papillae upper tarsal conjunctiva, hyperemia, chemosis	Watery discharge, papillae, hyperemia	Hyperemia, unilateral then bilateral mucopurulent/purulent discharge for bacterial and watery for viral; papillae (Bacterial); follicles (viral)	Hyperemia; mucopurulent discharge for bacterial, watery for viral	Hyperemia of bulbar conjunctiva, palpebral unaffected, watery discharge	Patchy or generalized uni- or bilateral hyperemia of bulbar conjunctiva, palpebral unaffected [episcleral vessel engorgement]	Hyperemia only in limbal area	Hyperemia, edema, mucous discharge, papules and follicles on palpebral conjunctiva
Sclera	N/A	N/A	N/A	N/A	Red-purple in color, thinned, edematous	Normal	N/A	N/A
Cornea	Corneal involvement rare	Scarring may occur without treatment	Infectious keratitis is considered a separate disease entity and is an emergency	Infiltrate or ulcer	Keratitis and peripheral keratopathy possible	Usually minimal	Corneal changes can occur as complication/sequela	Erosion, ulceration when severe
Eyelids	Thickening,	Blepharitis, redness, irritation;	Crusting-	N/A	N/A	N/A	N/A	Thickening, swelling,

	blepharitis	entropion/ectropion	bacterial>viral					excoriation
Limbus	N/A	N/A	N/A	N/A	N/A	N/A	Uni- or bilateral redness)+ to+++ isolate to this area	N/A

Table 3: Differential diagnosis of ocular allergy – physical findings

Legend: DED, dry eye disease; DITC, drug-induced toxic conjunctivitis; ES, episcleritis; GPC, giant papillary conjunctivitis; IS, Iritis; IFC, infectious conjunctivitis; K, keratitis; N/A, not affected; S, scleritis. +/- = may be present or absent; += mild; ++= moderate; +++= severe.

Have you	All of the	Most of the	Half of the	Some of the	None of the
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experienced any of the following during the last week?	time (4)	time (3)	time (2)	time (1)	time (0)
Itchiness					
Redness					
Tearing (eyes watering)					
Swelling (puffy eyes)					

Table 4: Total Ocular Symptom Score (TOSS) questionnaire

Preservative Free Ocular Lubricants (Help with dry eye symptoms and wash away allergens)

Category	Brand Name	OTC/Rx	Dosing
CMC containing	Allergan: Refresh Optive, Refresh Optive Advanced, Refresh Tears Plus, Refresh Liquigel, Refresh Celluvisc. Thera Tears: Thera Tears	OTC	As needed
HPMC containing	Alcon: Tears Naturale Free, Bion Tears	OTC	As needed
Hyaluronic acid containing	JnJ: Blink tears. Hylo Eye Care: Hylo-Comod, Hylo-Tear, Hylo-Fresh, Hylo Gel, Hylo-Care, Hylo-Parin (also contains Heparin), Hylo-Dual	OTC	3 times/day as needed
Glycerin containing	Oasis Tears: Oasis Tears, Oasis Tears Plus. Allergan: Refresh Optive, Refresh Optive Advanced, Refresh Digital	OTC	As needed
Mineral oil/petrolatum containing (ointments)	Akon: Akwa tears. Allergan: Refresh PM, Bausch Health: Soothe XP. Alcon: Systane Nighttime	OTC	qd at bedtime
Polyethylene glycol containing	JnJ: Blink tears. Alcon: Systane, Systane Ultra.	OTC	As needed
PVA containing	Refresh classic, Optics mini drops	OTC	As needed
Selected artificial tears by viscosity			
Low viscosity	Mid viscosity	High viscosity	Emulsion
Alcon: Systane Ultra and Classic, Tears Naturale Allergan: Refresh Tears, Refresh Optive, Refresh Plus, Refresh Relieva Thera Tears: Theratears JnJ: Blink tears	Allergan: Refresh Gel drops, Refresh Liquigel Alcon: Systane Gel drops	Allergan: Refresh Celluvisc, Refresh PM Alcon: Systane Nighttime (eye ointment)	Bausch Health: Soothe XP Allergan: Refresh Mega 3, Refresh Optive Advanced, Refreah Digital Alcon: Systane Balance, Systane Complete Santen: FreshKote

Table 5. Preservative-free ocular lubricants and selected artificial tears by viscosity

Ocular Medications – Decongestants, Antihistamines and Multi-action						
Generic	Brand Name	OTC/Rx	Adverse Effects/Limitations	Notes	Dosing	Pregnancy Category Former/Current
Decongestants						
Naphazoline	Akorn: AK-Con. Novartis: Vasocon. Allergan: Albalon	OTC	Conjunctivitis medicamentosa, rebound hyperemia, burning, tachyphylaxis, mydriasis	Contraindicated in narrow angle glaucoma, often overused by patients	qid	C/ Fetal risk cannot be ruled out
Tetrahydrozoline HCL	JnJ: Visine	OTC			qid	C/ Fetal risk cannot be ruled out
Decongestant and Antihistamine combination						
Naphazoline/Antazoline	Novartis: Vasocon-A	OTC	Burning, short duration of action, limited potency, mydriasis, chemosis	Contraindicated in narrow angle glaucoma, often overused by patients	1-2 drops qid	C/ Fetal risk cannot be ruled out
Naphazoline/Pheniramine	Alcon: Naphcon A Bausch Health: Opcon A. JnJ: Visine A	OTC			1-2 drops qid	C/ Fetal risk cannot be ruled out
Antihistamine						
Emedastine 0.05%	Alcon: Emadine	Rx	Local irritation, burning, stinging, sedation, headache	Longer duration of action than 1 st generation topical antihistamines, more effective than systemic antihistamines, need frequent dosing	1 drop qid; ≥ 3 years of age	C/ Fetal risk cannot be ruled out
Levocabastine 0.05%	Novartis: Livostin	Rx			1 drop qid; ≥ 12 years of age	C/ Fetal risk cannot be ruled out

Antihistamine and additional mechanism of action (Dual or Multi-action)						
Alcaftadine 0.25%	Allergan: Lastacast	Rx	Bitter taste, sedation, stinging, burning, headache, nasopharyngitis	H1, H2 and H4 antagonistic properties	1-2 drops qd; ≥ 3 years of age	B/ Fetal risk cannot be ruled out
Azelastine 0.05%	Meda: Optivar	Rx		Selective 2nd generation H1RA, inhibits PAF, blocks expression of ICAM-1, has H2-blocking properties	1 drop bid; ≥ 3 years of age	C/ Fetal risk cannot be ruled out
Bepotastine 1.5%	Bausch Health: Bepreve	Rx		H1-selective antagonist, eosinophil modulating, MCS, alleviates symptoms of AR	1 drop bid; ≥ 3 years of age	C/ Fetal risk cannot be ruled out
Epinastine 0.05%	Allergan: Elestat	Rx		H1RA, MCS, H2 antagonism	1 drop bid; ≥ 3 years of age	C/ Fetal risk cannot be ruled out
Ketotifen 0.025%	Bausch Health: Alaway Schering- Plough: Claritin eye, Novartis: Zaditor	OTC		Inhibits leukotrienes, eosinophil activation, cytokine release, H1RA, MCS. Additional side effects: Conjunctival injection, rhinitis, headache	1 drop Bid; ≥ 3 years of age	C/ Fetal risk cannot be ruled out
Olopatadine 0.1%	Alcon: Patanol	Rx		H1 selective antagonist, MCS. 0.7% concentration has superior	1-2 drops bid to qid; ≥ 3 years of age	C/ Fetal risk cannot be ruled out
Olopatadine 0.2%	Alcon:	Rx			1-2 drops	

	PataDay			efficacy when compared to lower concentrations	qd; ≥ 3 years of age	
Olopatadine 0.7%	Alcon: Pazeo	Rx			qd	
Cetirizine 0.24%	Santen: Zerviate	Rx	Redness, instillation site pain, reduced visual acuity	None	1 drop bid; ≥ 2 years of age	B/ Fetal risk cannot be ruled out

Table 6: Ocular Medications – Decongestants, Antihistamines and Multi-action

Legend: AR, allergic rhinitis; ICAM, intercellular adhesion molecule; MCS, mast cell stabilizing; OTC, over the counter; PAF, Platelet Activating Factor; RA, Receptor Antagonist; Rx, prescription medication

Ocular Medications – Mast cell stabilizers, NSAIDs, steroids and calcineurin inhibitors

Generic	Brand Name	OTC/Rx	Adverse Effects/Limitations	Notes	Dosing	Pregnancy Category Former/Current
Mast Cell Stabilizer						
Cromolyn 4%	Bausch Health: Crolom, Opticrom	OTC	Require pre-loading, frequent instillation, stinging, burning, redness, rhinitis, cold/flu symptoms		1-2 drops, 4-6 times a day; ≥ 2 years of age	C/ Fetal risk cannot be ruled out
Lodoxamide 0.1%	Alcon: Alomide	Rx			1-2 drops qid; ≥ 2 years of age	B/ Fetal risk cannot be ruled out
Nedocromil	Allergan: Alocril	Rx			1-2 drops bid; ≥ 3 years of age	B/ Fetal risk cannot be ruled out
Pemirolast 0.1%	Santen:Alamast	Rx			1-2 drops qid	C/ Fetal risk cannot be ruled out
NSAIDs						
Ketorolac	Allergan: Acular	Rx	Discomfort, stinging, burning	Cross reactive with other NSAIDs, use in caution in patients with aspirin/NSAID sensitivity	1 drop qid; ≥ 12 years of age	C/ Fetal risk cannot be ruled out
Steroids						
Fluorometholone	Allergan: FML 0.1%, FML Forte 0.25%	Rx	Increased IOP, Cataract formation, secondary ocular infection, contraindicated in superficial viral infections	Requires close monitoring by eye care specialist	Indicated as 1-2 drops qid; eyecare professionals prefer bid; ≥ 3 years of age	C/ Fetal risk cannot be ruled out
Loteprednol 0.2%	Bausch Health: Alrex	Rx	Increased IOP, but better than older agents.	Decreased cataract formation risk as compared to older topical steroids, requires close		C/ Fetal risk cannot be ruled out
Loteprednol 0.5%	Bausch Health: Lotemax	Rx	Headache, pharyngitis, rhinitis			

				monitoring by eye care specialist		
Calcineurin Inhibitors						
Cyclosporine 0.05%	Allergan: Restasis	Rx	Burning, foreign body sensation, hypersensitivity reaction	FDA approved only for dry eye syndrome, approved in Europe by EMA in July 2018 for severe VKC	1 drop bid	C/ Fetal risk cannot be ruled out
Tacrolimus 0.03% and 0.1% ointment	Leo: Protopic	Rx	Burning, risk of local infection, neoplasm	Severe AKC or VKC refractory to other treatment, approved for VKC in Japan	Off -label use, second- line short term therapy, thin layer topical application to eyelid or to conjunctival sac; ≥ 2 years of age	C/ Fetal risk cannot be ruled out

Table 7: Ocular Medications –Mast cell stabilizers, NSAIDs, steroids and calcineurin inhibitors

Legend: AKC, atopic keratoconjunctivitis; EMA, European Medicines Agency; FDA, Food and Drug Administration; IOP, intraocular pressure; NSAID, Non-steroidal anti-inflammatory drug; OTC, over the counter; Rx, prescription medication; VKC, vernal keratoconjunctivitis

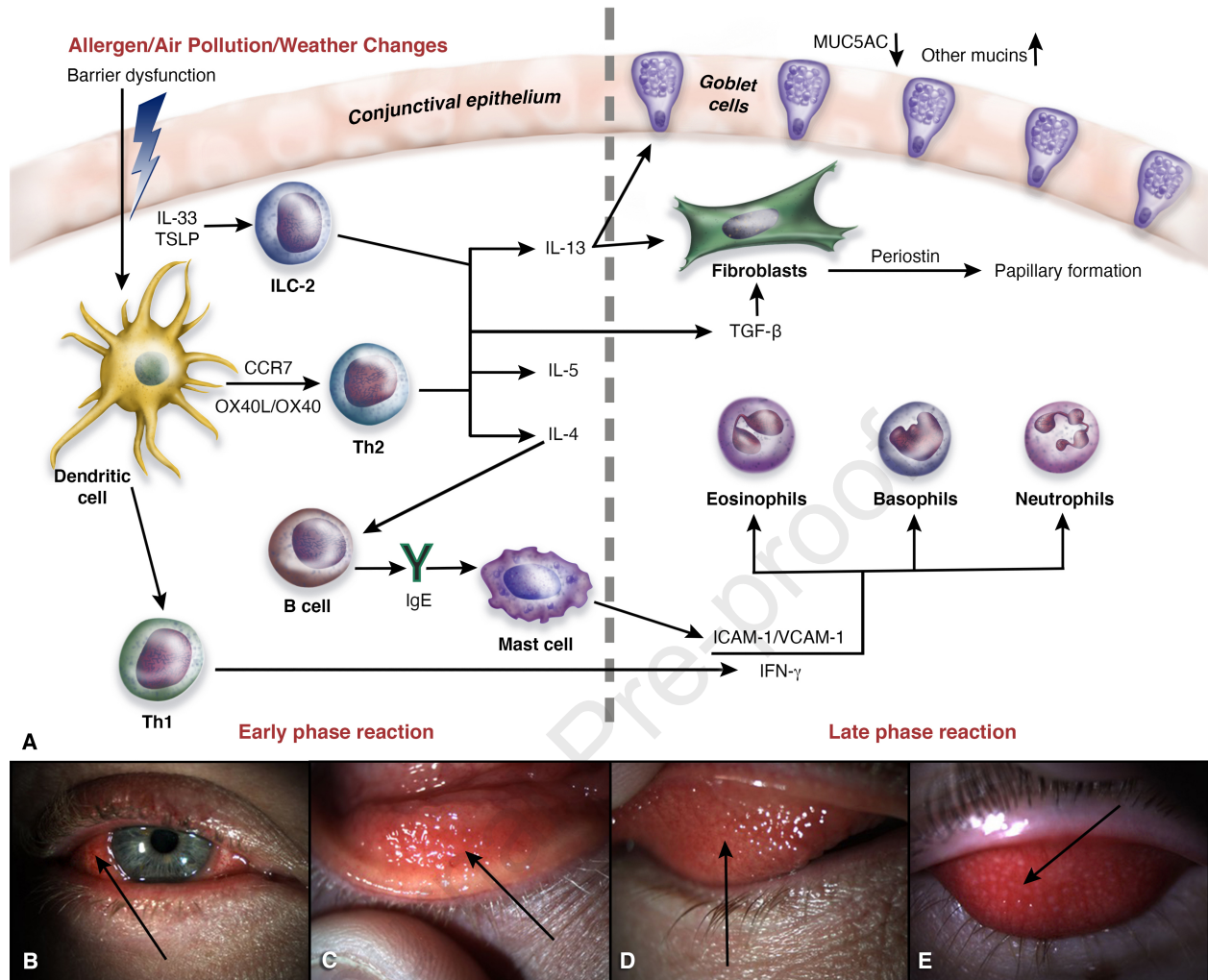


Figure 1: Pathogenesis of early and delayed phase responses in allergic conjunctivitis (A) and clinical presentation of allergic conjunctivitis including ocular hyperemia (B), follicles (C), papillae and follicles (D) and papillary response (E). CCR, CC chemokine receptor; ICAM, intercellular adhesion molecule; IFN, interferon; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; MUC, mucin; OX40, synonym of CD134 (CD, cluster of differentiation); OX40L, OX40 Ligand, synonym of CD252; TGF, transforming growth factor; Th, T helper cell; TSLP, thymic stromal lymphopoietin; VCAM, vascular cell adhesion molecule. Clinical Photos B-E courtesy of Dr. Jacob Lang, OD.

Key Messages:

- Ocular allergy is recognized as a heterogeneous collection of IgE and non-IgE mediated diseases.
- IgE-mediated ocular allergies include seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC)¹, vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC). Non-IgE mediated ocular allergies and hypersensitivities include contact blepharoconjunctivitis (CBC), giant papillary conjunctivitis (GPC), irritative conjunctivitis and blepharitis.
- Four cardinal symptoms characterize ocular allergies: redness, itchiness, swelling, and watering (tearing), with several symptoms overlapping with dry eye disease.
- Allergological workup (skin prick testing, serum-specific IgE measurements, conjunctival provocation testing and patch testing) is helpful in confirming a causative allergic mechanism.
- Newer topical corticosteroid formulations such as loteprednol have not been shown to increase the risk of cataracts unlike older corticosteroids.
- Successful treatment usually involves a combination of avoidance of allergic triggers, topical and/or oral medications and in some cases, allergy immunotherapy.