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Review

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Ocular Allergy Within the Framework of the EAACI Nomenclature of Allergic Diseases and Hypersensitivity Reactions

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ABSTRACT

Ocular allergy encompasses a heterogeneous group of diseases with overlapping clinical features and complex immunopathological mechanisms. This often creates challenges in classification and, consequently, in optimizing patient management. The nomenclature published in 2023 by the European Academy of Allergy and Clinical Immunology (EAACI) addresses these issues by redefining these conditions and linking clinical phenotypes and environmental modifiers to underlying types of hypersensitivity. This framework enhances diagnostic precision and supports mechanism-guided management. This article applies the EAACI approach based on hypersensitivity types to ocular allergy. The examples addressed include seasonal and perennial allergic conjunctivitis, driven mainly by type I and IV hypersensitivity reactions; vernal and atopic keratoconjunctivitis, involving mixed type I, IVb and IVa pathways; giant papillary conjunctivitis, a tissue-driven type V reaction; and contact blepharoconjunctivitis, a type IVa delayed hypersensitivity reaction with additional components. Distinct endotypes—such as local or acute allergic conjunctivitis, dupilumab-induced ocular disease, and vernal keratoconjunctivitis/atopic keratoconjunctivitis overlap—further illustrate heterogeneity, with the ocular surface microbiome emerging as a modifier. Diagnostics are increasingly aligning with mechanisms, and the EAACI framework translates this complexity into a mechanism-indexed map; this supports the selection of responders for targeted interventions while minimizing overtreatment.

Keywords: Allergic conjunctivitis; EAACI nomenclature; endotypes; hypersensitivity reactions; ocular allergy; ocular immune responses; keratoconjunctivitis

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INTRODUCTION

In 2012, the European Academy of Allergy and Clinical Immunology (EAACI) published a Position Paper proposing a classification system for allergic eye diseases. This classification included: seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), giant papillary conjunctivitis (GPC), contact blepharoconjunctivitis (CBC) also called contact/drug-induced dermato-conjunctivitis (CDC).[1]

This taxonomy was based on the Gell and Coombs classification of hypersensitivity reactions. Type I (immediate) hypersensitivity was identified in SAC and PAC. VKC and AKC were characterized by a mixed pathomechanism involving both type I and type IV hypersensitivity reactions. CBC was associated primarily with a type IV (delayed) hypersensitivity mechanism. Additionally, GPC was categorized as a non-immune hypersensitivity reaction, often triggered by mechanical irritation rather than an immune response.[2]

Since the release of the 2023 EAACI Position Paper on nomenclature of allergic diseases[3] and hypersensitivity reactions, along with new insights into ocular inflammatory cells and cytokine profiles, epithelial barrier and ocular microbiome, experts in ocular allergy have begun to refine a pathophysiology-based classification by incorporating disease phenotypes and endotypes. This evolving framework is expected to enhance diagnostic accuracy—particularly in complex cases such as AKC, VKC, and CBC—and to support more targeted therapeutic strategies, including the use of biologic agents.

NEW CLASSIFICATION OF OCULAR ALLERGIC DISEASES WITHIN THE FRAMEWORK OF THE EAACI NOMENCLATURE OF ALLERGIC DISEASES AND HYPERSENSITIVITY REACTIONS

The currently proposed classification of ocular allergic diseases is summarized in the **Figure** and the **Table**. This framework clarifies overlaps (*e.g.*, SAC/PAC and VKC/AKC) and supports a more precise diagnosis and treatment selection.

SAC

SAC (sometimes described as intermittent allergic conjunctivitis, IAC) is the most common form of ocular allergy, accounting for approximately 60%–90% of all cases. SAC is generally mild-to-moderate and rarely threatens vision (unlike VKC/AKC), though symptoms can be very bothersome. It manifests as an inflammation of the conjunctiva primarily triggered by outdoor allergens, specifically pollen from various plants during specific seasons, typically peaking during spring and summer. Symptoms such as itching, redness, swelling of the eyelids, conjunctival hyperemia, and excessive tearing often coexist with the symptoms of allergic rhinitis.[4]

SAC is mediated mainly by a type I and IVb hypersensitivity reaction - type 2 immune response (T2) involving type 2 helper lymphocytes (Th2), B cells and group 2 innate lymphoid cells (ILC2s). These cells drive the production of T2 interleukins (IL-4, IL-5, IL-9, and IL-13),

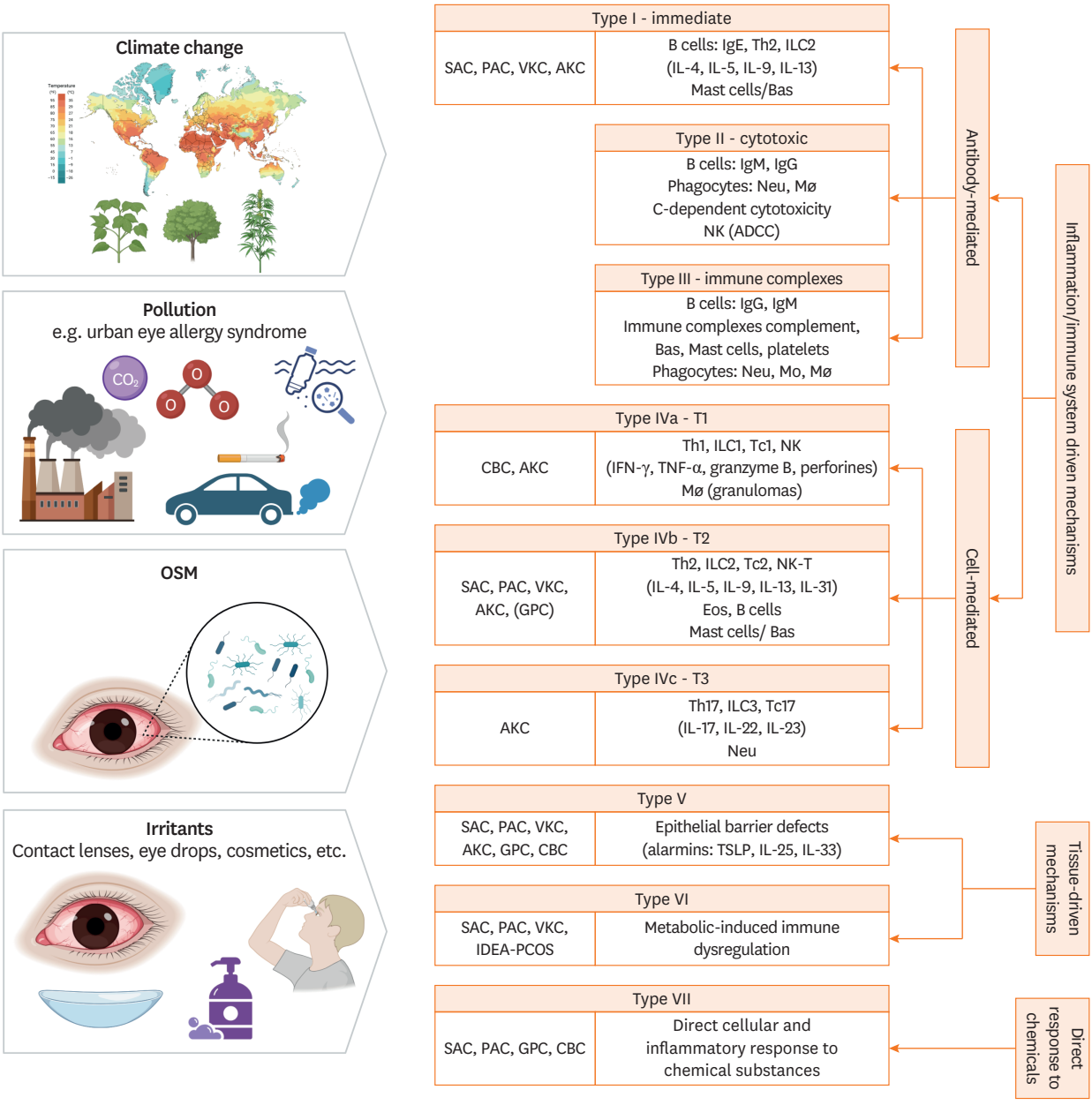

Figure. EAACI framework linking ocular-allergy entities to underlying mechanisms while highlighting external and tissue-driven modifiers that shift severity and endotypes. Left: modifiers that aggravate or shape disease expression—climate change (increasing allergen load and immunogenicity; prolonged season length; heat and UV stress, extreme weather events, sand and dust storms), environmental pollution/urban exposure (barrier injury, adjuvant effect, and epithelial barrier dysfunction), increased use of irritants (contact lenses, cosmetics, and eye drops) and ocular surface microbiome dysbiosis. Right: ocular allergy entities are arranged within the EAACI nomenclature and mapped to hypersensitivity types (I–VII), highlighting that identifying the dominant pathway allows treatment to be tailored to the mechanism.
EAACI, European Academy of Allergy and Clinical Immunology; UV, ultraviolet; SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis; IgE, immunoglobulin E Th2, type 2 helper lymphocytes; ILC2, group 2 innate lymphoid cell; IL, interleukin; NK, natural killer; ADCC, antibody-dependent cellular cytotoxicity; CBC, contact blepharoconjunctivitis; IFN, interferon; TNF, tumor necrosis factor; OSM, ocular surface microbiome; GPC, giant papillary conjunctivitis; TSLP, thymic stromal lymphopoietin; IDEA-PCOS, itchy-dry eye in polycystic ovary syndrome.

promoting allergen specific immunoglobulin E (sIgE) synthesis, and degranulation of effector cells, mast cells and basophils, with release of preformed and newly formed pro-inflammatory mediators (histamine, tryptase, leukotrienes, prostaglandins, *etc.*).[5,6]

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Table. Ocular allergy entities in the EAACI nomenclature: hypersensitivity types, dominant immune pathways, key phenotypes, and modifiers

Entity	EAACI hypersensitivity types	Dominant immune pathway/endotype	Sub-phenotypes
SAC & PAC	**Type I & IVb (T2)** **Type V**, VI, VII as initiator and modifier in polluted air/irritants	IgE–Th2; ILC2; mast cells/basophils; IL-4/5/9/13, histamine-mediated response; Barrier dysfunction with pollutants/irritants; Dysbiosis conjunctival microbiome; Direct aeroallergen-induced stimulation of nociceptors	LAC; AAC; PAC can **coexist with SAC** (perennial baseline + seasonal flares); Urban eye allergy syndrome (can aggravate)
VKC	**Type I mixed with type IVb** Initiator and modifier: **type V**, type VI	Mixed T2/eosinophilic with Th2 T-cell component; Epithelial alarmins (TSLP, IL-25, IL-33); Neurogenic inflammation; Microbiome dysbiosis	Tarsal/limbal/mixed; Seasonal or perennial; Adult VKC-like syndrome (often coexist with asthma); VKC/AKC overlap; VKC/AKC with keratoconus; VKC+HIV; Urban eye allergy syndrome (can aggravate)
AKC	**Type IVb (dominant) + type I** Possible **T1/T3 skew (type IVa/c)** Initiator and modifier: **Type V**	Heterogeneous (T2-, T1/T3-, or mixed profiles); IL-4/IL-13, IL-6/IL-17 in subsets, neutrophils, goblet-cell loss	Adult vs childhood phenotype; VKC/AKC overlap; Risk of **DIOSD** under dupilumab/tralokinumab (often T1/T3-shift with neutrophilic features); Urban eye allergy syndrome (can aggravate)
GPC	**Type V (tissue-driven)** Co-factors **Type VII** (irritants) Occasional **T2 overlay**	Mechanical microtrauma from lenses/prostheses/sutures; barrier dysfunction; irritant preservatives/debris can amplify	Possible *T2* overlay endotype
CBC	**Type IVa (T1-cell delayed)** with **type VII (irritant)** Often **type V** barrier component Type VI (IDEA-PCOS)	Hapten allergy (e.g., drugs/preservatives/cosmetics) and/or direct chemical irritation; non-IgE; androgen imbalance/low-grade inflammation	IDEA-PCOS

Epithelial barrier defect (type V) may act as an initiator of various pathogenetic pathways, including activation of the innate immune response through epithelial alarmins. The ILCs modulate dendritic cell phenotype to initiate a T1, T2 or a T3 immune response. The OSM acts as a modifier of tissue-driven pathways (type V and VI) by influencing barrier function and local immune responses. Dysbiosis (reduced diversity, loss of commensals, overgrowth of pathobionts), thereby modulate severity and treatment response.
EAACI, European Academy of Allergy and Clinical Immunology; SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; IgE, immunoglobulin E Th2, type 2 helper lymphocytes; ILC2, group 2 innate lymphoid cell; IL, interleukin; LAC, local allergic conjunctivitis; AAC, acute allergic conjunctivitis; VKC, vernal keratoconjunctivitis; TSLP, thymic stromal lymphopoietin; AKC, atopic keratoconjunctivitis; HIV, human immunodeficiency viruses; DIOSD, dupilumab-induced ocular surface disease; GPC, giant papillary conjunctivitis; CBC, contact blepharoconjunctivitis; IDEA-PCOS, itchy-dry eye in polycystic ovary syndrome.

Within SAC, distinct immunological subendotypes have been identified. One such variant is local allergic conjunctivitis (LAC), also known as entopy, in which the allergic inflammatory response is confined just to the conjunctival tissue and regional lymphoid structures, without IgE systemic sensitization.[7] Another phenotype is acute allergic conjunctivitis (AAC), which, despite sharing the same underlying type I hypersensitivity mechanism as SAC, presents with a different clinical course.[1] AAC is also described as an explosive periocular reaction,[8] which is characterized by rapid, intense swelling of the ocular conjunctiva, often accompanied by eyelid oedema that can temporarily close the palpebral fissure. It typically results from massive exposure to a sensitizing allergen and is primarily triggered by the release of histamine. Although the presentation may appear severe, AAC is self-limiting, does not cause structural damage to the eye, and generally resolves spontaneously within 24 to 48 hours after allergen exposure ceases.

Outdoor pollutants and irritants can potentiate pollen exposure by increasing allergenicity and acting as adjuvants to type I/T2 responses—an effect termed urban eye allergy syndrome (see PAC).

PAC

PAC is a chronic inflammation of the conjunctiva caused primarily by year-round exposure to indoor allergens such as dust mites, pet dander, mold spores, and cockroach, presenting with symptoms similar to SAC.[9] PAC can coexist with SAC; in polysensitized patients this often appears as a perennial baseline with superimposed seasonal flares during high-exposure to pollen periods.[10] PAC is driven by type I and IVb hypersensitivity reactions involving the same inflammatory cells and cytokines, as SAC, and exhibits distinct endotypes. As in SAC, we distinguish the endotype of local reaction (entopy/LAC) in about 30% of cases and AAC.

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PAC is particularly susceptible to the impact of environmental pollutants such as exhaust fumes, nitrogen oxide (NO), nitrogen dioxide (NO_2), carbon monoxide (CO), carbon dioxide (CO_2), volatile organic compounds (VOCs), particulate matter ($PM_{2.5}$ and PM_{10}), diesel exhaust particles (DEPs), microplastics, and nanoparticles. These pollutants can exacerbate allergic responses by triggering epithelitis, enhancing mucosal permeability and promoting inflammatory pathways—disrupting the conjunctival epithelial barrier, making allergens more likely to penetrate, directly activating epithelial cells to release pro-inflammatory mediators and alarmins, inducing oxidative stress, and acting as adjuvants—it has been described as urban eye allergy syndrome with an associated type V reaction (according to the new EAACI nomenclature by Jutel *et al.*[3]) in response to adverse environmental factors.[8,11,12] Other components, such as products of coal, oil, and sulfur dioxide (SO_2) combustion, can disrupt the tear film. Ozone (O_3) irritates the conjunctiva, disrupts the tear film, and increases pollen allergenicity.[13,14] Consequently, the clinical picture may be dominated by conjunctival irritation—especially foreign-body sensation—rather than the classic allergic symptoms described above. Various other irritants such as soap, shampoos, contact lenses, eye drops, cosmetics, including make-up products, can act similar to pollutants in inducing the epithelial barrier defect.[15,16]

The epithelial barrier defect (type V hypersensitivity) plays an important role in the pathogenesis of both SAC and PAC. For example, SAC patients manifest symptoms within minutes after pollen exposure, pointing to a specific mechanism for the rapid transport of allergens through the barrier and into the tissue. Instillation of pollen shells rapidly induced a large number of goblet cell-associated antigen passages (GAPs) in the conjunctiva. Antigen acquisition by stromal cells, including macrophages and CD11b+ dendritic cells, correlated with surface GAPs formation. The rapid GAPs formation and antigen acquisition were suppressed by topical lidocaine or trigeminal nerve ablation, indicating that the sensory nervous system plays an essential role.[17]

Type VI hypersensitivity can also contribute to the pathogenesis of SAC and PAC. Alterations in the ocular microbiome may be significant in both conditions. Metagenomics shotgun sequencing showed that the conjunctival microbiome in patients with ocular allergy was distinct to the microbiome of healthy control subjects. Bacteria dominated the ocular surface microbiome (OSM) of all participants, with a lower inter-individual variation in alpha diversity of the allergic eye disease participants compared to healthy controls.[18] Unmyelinated C fibers on the ocular surface transmit histaminergic itch and can be directly activated by mast cell mediators. Allergen-complexed IgE also binds directly to high-affinity IgE receptor (FcεRI) expressed on peripheral neurons.

The conjunctival mucosa also contains transient receptor potential vanilloid 1 (TRPV1) (histamine-dependent) and transient receptor potential ankyrin 1 (TRPA1) (histamine-independent) neurons that enhance ocular pain and itch in allergic conjunctivitis. Environmental aeroallergens can also directly stimulate neuronal nociceptors to release inflammatory substances, accounting for type VII hypersensitivity.[19]

VKC

VKC is a chronic, bilateral inflammatory disease of the conjunctiva and cornea that typically begins in the first decade (male-predominant) but can persist into or arise in adulthood.[20] Clinically, it presents with recurrent, often spring-summer flares (seasonal phenotype) or year-round (perennial phenotype) marked by intense itching, photophobia, tearing, and

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stringy mucus; hallmark signs include giant "cobblestone" tarsal papillae, limbal gelatinous thickening with Horner–Trantas dots, and corneal involvement (punctate keratitis, shield ulcers) that can threaten vision.[21] Ocular surface remodeling leads to severe suffering and complications, such as corneal ulcers/scars. Conjunctival injections are mostly severe with thick mucus ropy discharge. VKC can occur under three forms: limbal, tarsal, and mixed. Additional clinical variants are recognized, including adult-onset VKC, VKC–AKC overlap, human immunodeficiency viruses (HIV)-associated VKC in children receiving antiretroviral therapy, and VKC/AKC associated with keratoconus.[22] Adult VKC-like syndrome is the clinical features of VKC; however, it occurs only in young adults and also often coexists with bronchial asthma.[23]

Pathophysiology is mixed: in the EAACI nomenclature, VKC reflects a combination of type I (IgE/Th2; mast cells and eosinophils) and type IVb (Th2 T-cell-mediated) hypersensitivity, with additional tissue-driven processes (type V; epithelial barrier dysfunction), neurogenic inflammation and microbiome driven pathogenetic pathways (type VI). Eosinophils are the predominant cells found in the tears and eye discharge. Epithelial alarmins (thymic stromal lymphopoietin, IL-25, and IL-33) act upstream to amplify the cascade, and IgE involvement is documented in ~40%–75% of cases.[24-26]

Urban eye allergy syndrome (pollution- or irritant-related, tissue-driven modifier; type V): foreign-body sensation may dominate; can aggravate VKC.[27]

AKC

AKC is a chronic, sight-threatening inflammatory disease of the ocular surface closely linked to atopic dermatitis (AD). Core manifestations include itching/burning, redness, tearing, stringy mucus, photophobia; tarsal papillae; lid margin inflammation/blepharitis; punctate keratopathy; (in longstanding disease) corneal complications. It typically presents after adolescence—peaking between ages 30–50—and may persist for decades.[22] Disease severity tends to increase with earlier and more severe AD; by contrast, a childhood phenotype (< 16 years) has been described with a generally milder course and a lower risk of corneal involvement.[28,29] In addition, a VKC–AKC overlap phenotype is recognized: in patients with AD, ocular disease may present as mild, seasonally driven VKC-like episodes or as severe, perennial AKC-like inflammation. An AKC/VKC overlap with keratoconus is also described, typically affecting adolescents; it is often familial and characterized by progressive astigmatism and Munson's sign (V-shaped protrusion of the lower eyelid on downgaze), with ~50% showing predominance of IL-4 and IL-13-driven (type 2 inflammation [T2]).[24]

AKC exhibits mixed hypersensitivity, with type I involvement ~30%–40% but type IV (T-cell-mediated) mechanisms predominating, however with a different inflammatory-cell configuration.[30] This becomes clinically relevant when starting AD biologics—dupilumab (anti-IL-4/IL-13) or tralokinumab (anti-IL-13)—because AKC endotypes are heterogeneous: about 17% T2 type-predominant, 17% T1/T3-type-predominant (type IVa/c), and the remainder mixed/variable.[31] These findings clarify the mechanism behind the relatively frequent ocular adverse lesions seen after treatment with dupilumab—typically milder and less common with tralokinumab—termed dupilumab-induced/associated ocular surface disease (DIOSD/DAOSD).[32] Clinically, DIOSD/DAOSD presents with progressive ocular itching and burning of the conjunctiva, worsening dry-eye symptoms with tearing, and eyelid-margin inflammation/blepharitis with a tendency to scar; additional signs include limbal swelling (limbitis) and a papillary/vesicular conjunctival reaction. Pathophysiological,

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it often reflects a shift toward T1/T3 immune response in AKC, with elevated IL-6 and IL-17, a tendency for corneal vascularization, and the appearance of new contact allergies.[33,34] In patients with a T1/T3-skewed or mixed profile, neutrophilic conjunctivitis with goblet-cell loss and tear-film instability may develop, and severe cases can necessitate modifying or discontinuing the biologic despite good cutaneous control of AD.[35]

If, during AD biologic therapy (dupilumab and tralokinumab), ocular inflammation follows a T1/T3 or mixed (variable) profile, patients may develop neutrophilic conjunctivitis with goblet-cell loss and tear-film instability. In severe cases, these ocular events may necessitate modifying or discontinuing the biologic, despite good cutaneous responses.[35] Because tear cytokine testing is not widely available, an ophthalmology consultation is recommended before initiating (or soon after starting) these agents to establish a baseline and mitigate risk, evaluating the ocular organ for dry eye syndrome, the presence of Demodex or Malassezia in the periorbital skin.

Urban eye allergy syndrome (pollution-driven, tissue-based modifier; type V), foreign-body sensation often predominates and may exacerbate AKC.

GPC

GPC is characterized by giant tarsal papillae of the upper eyelid with itching, ropy mucus, contact-lens intolerance, and fluctuating blur; it is most commonly seen in contact-lens wearers, but also with ocular prostheses or exposed sutures.[36] The primary driver is repeated mechanical friction from a foreign surface (*e.g.*, lens edges or deposits/biofilms), with risk increased by infrequent lens replacement, poor hygiene, and non-disposable materials. Lens chemistry and surface deposits also contribute significantly to the pathogenesis.[37] The appearing papillae of the eyelid conjunctiva make it impossible to wear contact lenses at least during the acute phase of the disease.

GPC is classified as an ocular hypersensitivity disorder in which the primary mechanism is tissue-driven epithelial irritation and dysfunction (type V hypersensitivity) caused by mechanical microtrauma. Direct chemical or irritant exposures—such as care-solution preservatives or debris—can act as type VII co-factors, exacerbating inflammation. However, in some patients, particularly those with a T2-skewed endotype (Th2/IgE-biased), a superimposed T2 inflammatory component (type I/IVb) may develop, accounting for the presence of eosinophils and mast cells on histology and the partial responsiveness to anti-allergic eye drops, resulting in a mixed-pathway phenotype.[38]

CBC

CBC—also termed CDC—is inflammation of the eyelid skin and conjunctiva provoked by external agents (topical medications, cosmetics, contact-lens solutions, adhesives, and occupational agents).[38] Clinically, it presents with itch/burn, tearing, conjunctival hyperemia/chemosis, follicular or papillary changes, and eyelid dermatitis (erythema, oedema, scaling, and fissuring); irritant flares are immediate, whereas allergic flares peak after hours to days.

Unlike GPC, which is primarily mechanical injury, CBC is driven by chemicals and preservatives and relies on identifying and eliminating the culprit exposure (often switching to preservative-free products or stopping the offending cosmetic). Key haptens include ophthalmic drugs/preservatives such as aminoglycosides (neomycin/tobramycin), brimonidine/apraclonidine, dorzolamide, atropine/mydriatics, thimerosal, benzalkonium

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chloride, chlorhexidine, and polyhexamethylene biguanide/polyquaternium-1, as well as cosmetic allergens like fragrance mix, balsam of Peru, formaldehyde-releasers, isothiazolinones, and acrylates/cyanoacrylate in lash glues.[39,40]

Under the EAACI nomenclature, it is classified primarily as a type IVa hypersensitivity reaction (allergic, T-cell-mediated) to haptens, often accompanied by type VII direct irritant effects and a type V tissue-driven barrier component resulting from repeated exposure.

The itchy-dry eye

Ocular allergy and dry eye disease (DED) have a significant clinical overlap. Alterations in the tear film, epithelial barrier, and corneal innervation have been described in ocular allergy and can pave the way for DED. Conversely, DED may facilitate or worsen allergic reactions in predisposed patients.[41]

Itchy-dry eye in polycystic ovary syndrome (IDEA-PCOS),[42] characterized by persistent pruritus and conjunctival congestion in women with PCOS, aligns primarily with type VI (metabolic/endocrine, tissue-driven) and secondarily with type V (barrier dysfunction) according to the new EAACI nomenclature. Androgen imbalance and low-grade inflammation in PCOS can impair meibomian gland function and destabilize the tear-film lipid layer, resulting in reduced tear break-up time, mucus strings, foreign-body sensation, and contact lens intolerance.[43,44] Therefore, management focuses on tear-film lubrication and lid hygiene rather than anti-allergic therapy.

OSM AS A MODIFIER OF OCULAR ALLERGY

The OSM modulates disease via tissue-driven pathways—specifically type V and VI (epithelial barrier dysfunction and alarmin release)—rather than representing a separate hypersensitivity type. The OSM comprises the microbial communities of the eyelid skin/margins, conjunctiva, and corner.[45] In health, it is dominated by members of *Proteobacteria*, *Actinobacteria*, and *Firmicutes*, with frequent genera such as *Corynebacterium*, *Pseudomonas*, *Staphylococcus*, *Streptococcus*, and *Acinetobacter*.[46] Dysbiosis—reduced diversity, loss of commensals, overgrowth of pathobionts, or altered metabolic output—can impair barrier function and skew local immunity, contributing to eyelid inflammation, dry eye, Stevens-Johnson syndrome, and infectious keratitis.[47] By disrupting epithelial integrity and exposing the ocular surface to microbial metabolites and lipopolysaccharides that activate TRPV1/TRPA1 sensory neurons, dysbiosis may also amplify neurogenic inflammation, linking microbiome-driven mechanisms to type V–VII pathways.

In ocular allergy specifically, SAC/PAC cohorts show lower microbial diversity and a higher *Bacillus*/*Acinetobacter* ratio versus controls, proposed as a biomarker of allergic inflammation; PAC and SAC may also differ in specific taxa (e.g., reports of *Kocuria* and *Propionobacterium acnes* species-colonization were observed in the perennial allergic conjunctivitis group).[48] In more severe phenotypes (VKC/AKC), studies describe quantitative shifts with increases in selected genera (e.g., *Moraxella*, *Morganella*, *Blautia*) and decreases in others (e.g., within *Proteobacteria*), alongside higher abundance of *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Acinetobacter*, *Neisseria*, and *Haemophilus*; enrichment of *Streptococcus* has been proposed as a marker distinguishing VKC/AKC from milder allergic conjunctivitis.[18,48-50]

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Using high throughput 16S rRNA sequencing a higher abundance of *Moraxella* sp. in the ocular surface of VKC subjects was reported compared to healthy controls. In addition to *Proteobacteria*, *Firmicutes*, and *Actinobacteria*, which were found in the core microbiomes of all participants in this study, *Bacteroidetes* and *Fusobacteria* were also found in the samples obtained from VKC patients. The authors hypothesized that such alterations in the ocular surface microbiome with the additional presence of gram-negative bacteria in VKC subjects may potentially induce a lipopolysaccharide-induced inflammatory response, suggesting a molecular mechanism for VKC (type VI hypersensitivity). For the fungal microbiome, *Malasseziaceae* was observed to be significantly greater in abundance in patients with VKC compared to controls.[51] Conjunctival RNA sequencing transcriptomics showed an over-expression of pattern recognition receptors in VKC. Thus, the authors hypothesized that *Malasseziacea* interacts with these receptors, triggering a Th2-like response that is similar to that seen in atopic skin diseases.[52]

Overall, within the EAACI framework, these microbiome effects are best viewed as modifiers of local, tissue-driven hypersensitivity (type V and VI) that can influence ocular allergy endotypes (T1-, T2-, or T3-skewed), with therapeutic implications for barrier support—including preservative minimization—alongside standard local environmental care.

DIAGNOSTICS AND MANAGEMENT OF OCULAR ALLERGY WITHIN THE EAACI MECHANISTIC FRAMEWORK

Within the new EAACI mechanistic framework for hypersensitivity reactions encountered in allergic diseases, diagnostics and management are increasingly guided by underlying hypersensitivity types, tissue-driven pathways, and endotypes, linking clinical phenotypes to pathophysiology.[4]

Diagnostics

Tear-film evaluation is essential, particularly for distinguishing dry-eye contributions to ocular allergy. Common measures include the Schirmer test, tear break-up time, tear osmolarity, interferometry for lipid-layer thickness, and meniscometry (tear meniscus height/volume), with some tests reserved for specialist centers.[53] Visual acuity assessment is particularly important in VKC/AKC. Imaging modalities such as *in vivo* confocal microscopy (for corneal changes, early/late allergic phases, and treatment monitoring), laser scanning of the conjunctiva and meibomian glands, meibography, and anterior-segment ocular surface imaging provide additional mechanistic insights.[54]

The conjunctival allergen provocation test (CAPT) confirms causative allergens in SAC/PAC and identifies lead allergens for allergen immunotherapy (AIT).[55]

Tear IgE (total or specific) can be measured when available. Conjunctival sampling—via tear cytology, scrapings, impression cytology, or biopsy—supports diagnosis, with even a single eosinophil being highly suggestive, though absence does not exclude allergy. Useful T2 biomarkers include specific IgE, lactoferrin, matrix metalloproteinase-9, thymus and activation-regulated chemokine, eosinophil cationic protein, and IL-4/5/13.

Management

Treatment across ocular allergic diseases focuses on trigger' control and tiered anti-inflammatory therapy: immediate allergen/irritant avoidance (including cold saline rinses),

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topical second-generation antihistamine/mast-cell stabilizers (preferably preservative-free, often chilled), and oral antihistamines when rhinitis coexists.[10] AIT is considered when a causative allergen is documented (*e.g.*, pollen in SAC; house-dust mites or cat dander in PAC). Flares—especially in VKC/AKC—may require short courses of topical corticosteroids, with topical cyclosporine as steroid-sparing maintenance; nonsteroidal anti-inflammatory drug drops can be an alternative for symptom spikes.[56] Biologics are used within national programs in selected T2-high or comorbid cases: omalizumab (anti-IgE) and dupilumab (anti-IL-4Rα), tralokinumab (anti-IL-13) are listed, with mepolizumab/benralizumab/tezepelumab where asthma coexists.[26] AKC eyelid disease often adds topical tacrolimus and emollients. GPC emphasizes contact-lens holiday/material change, plus preservative-free lubricants and anti-histamine drops; severe VKC may need procedures (e.g., cryotherapy of papillae, sub-tarsal steroid injections, amniotic membrane, keratoplasty). DIOS/DAOSD (dupilumab-associated) is managed as dry eye with consideration of drug withdrawal if refractory.[57] Urban eye allergy syndrome follows dry-eye style measures and exposure reduction. CDC/CBC requires culprit withdrawal (patch-test guided), emollients, topical tacrolimus or short topical steroids; sedating antihistamines are occasional adjuncts.[12] Irritant conjunctivitis stresses no rubbing and simple barrier care, while IDEA-PCOS follows dry-eye/meibomian gland dysfunction measures with preservative-free antihistamine drops as needed.

CONCLUSION

Integrating diagnostics and treatment within the EAACI mechanistic framework allows clinicians to tailor interventions to underlying hypersensitivity types (I–VII), tissue-driven processes (V/VI/VII), and patient-specific endotypes, optimizing outcomes while reducing the risk of overtreatment. This shifts ocular allergy management from label-based practice to mechanism-guided management, giving healthcare professionals a clear, practical decision framework at the point of care.

A structured history, examination, and targeted tests (skin prick test/sIgE, patch testing, CAPT, tear-film metrics, cytology/biomarkers, and imaging) identify the dominant hypersensitivity pathway—type I/T2, type IVa, tissue-driven V/VI, or irritant VII—and clarify mixed presentations. This mechanistic mapping then guides therapy: allergen immunotherapy for IgE driven T2 disease, biologics for T2-high or multisystem cases, culprit withdrawal for type IVa, and barrier/environmental/microbiome strategies for tissue-driven or irritant pathways, enabling individualized, evidence-based care while minimizing overtreatment.

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Figure created in BioRender. Zemelka-Wiącek M (2025), https://BioRender.com/xpm8526. This study was financially supported by the Polish Ministry of Health subvention according to the number SUBZ.A020.25.023 from the IT Simple system from Wroclaw Medical University.

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