



Ocular Allergy:

A Scientific Review and Expert Case Debate

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TARGET AUDIENCE

- Allergists
- Ophthalmologists

ACTIVITY PURPOSE

Educate physicians on the various forms of ocular allergies as well as current management options and emerging treatment.

STATEMENT OF NEED

Allergic conjunctivitis is one of the most common conditions seen by ophthalmologists, optometrists, and allergists. During the past 40 years, both the incidence and prevalence of allergic conjunctivitis have risen exponentially, and they continue to rise. Numerous treatment strategies abound without any clear consensus from various clinical studies, creating a challenge for healthcare providers.

Current ocular allergy treatment options are effective only at mediating the symptoms, and these options have many different methods of action and modes of delivery. Allergists, ophthalmologists, and optometrists must

become better versed in the classification, severity indices, and various options available for treatment of ocular allergy and they must also become cognizant of the differences between the various subtypes of dry eye disease and ocular allergy. In addition, they must be able to recognize the severity of dry eye disease and ocular allergy.

LEARNING OBJECTIVES

After completing this enduring activity, participants should be able to:

- Differentiate between the various types of ocular allergies based on clinical presentation
- Individualize management options for ocular allergy based on disease severity, patient factors, and associated risks and benefits
- Describe the newer studies on the diagnosis and treatment of ocular allergy that are rapidly changing potential treatment algorithms

DESIRED RESULT/OUTCOME:

Ophthalmologists know and apply current treatment strategies through an individualized stepwise approach to optimize treatment outcomes in patients with ocular allergy.

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REVIEW
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Introduction

Allergies are said to affect up to 50 million Americans, and up to 40% of the global population has signs of allergies.¹⁻³ Ocular allergies involve the conjunctiva and often coexist with allergic rhinitis, atopic dermatitis, and/or allergic asthma.⁴ In the pediatric population, one study found that 32% of children with allergies had ocular symptoms as their sole manifestation.⁵ About 15% of the worldwide population is affected by ocular allergies, with increasing numbers in industrialized nations.⁵⁻⁷ In addition, the economic impact of allergies is significant—about \$5.9 billion is spent yearly on ocular allergy treatments.⁸

Most allergies treated by eye care specialists involve seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), with chronic vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC) comprising a much smaller percentage.⁹ The chronic forms may involve the lid, conjunctiva, and cornea and may necessitate comanagement with eye care specialists, allergists, dermatologists, and pediatricians. Chronic cases

patient health, a consensus on treatment strategies remains elusive.¹⁰ Current treatment options can be effective at addressing the symptoms of ocular allergy, at limiting inflammation, and at preventing damage to the ocular surface.^{11,12}

Pathophysiology of ocular allergy

At its most simplistic, an ocular allergic reaction follows the same pathophysiologic pathway as an allergic reaction in any other location: a type 1 hypersensitivity reaction is mediated by highly directed subsets of immunological mechanisms that predominantly involve mast cells and immunoglobulin E (IgE). When patients are exposed to an antigen, the antigen binds to the IgE molecules, crosslinking the molecules on the mast cell surface. Mast cells respond by releasing a large number of mediators of the allergic response that are preformed or synthesized de novo.

Histamine and eosinophil chemotactic factor are the predominant preformed mediators stored in mast cell granules. Prostaglandins and leukotrienes are synthesized

Ocular Allergy Diagnosis	Typical Causes	Secondary Causes
Seasonal allergic conjunctivitis	Aeroallergens: Spring: trees, pollen Summer: grass/weeds, some trees Fall: weeds, some trees	
Perennial allergic conjunctivitis	Animal dander, dust mites, feathers	Molds, yeast
Vernal keratoconjunctivitis	Multifactorial (IgE and Th2 [T helper 2] mediated with nonspecific triggers such as sun, dust, and wind); genetic	
Atopic keratoconjunctivitis	Multifactorial with stimulants such as stress, bacteria, aeroallergens, and food allergies	
Giant papillary conjunctivitis*	Trauma from sutures, glue, scleral buckles, prosthetic devices, and contact lenses (CLs)	Associated with CL use; mechanical irritation

*Not generally considered a true allergic response

Source: Luchs, Raizman, Shovlin, Wolf

may also induce ocular surface tissue remodeling; safe, long-term treatment regimens for severe cases are lacking.

SAC and PAC are localized type 1 hypersensitivity reactions with fewer eosinophils than the more chronic forms. Typical presentation includes hyperemia, chemosis, watery discharge, tearing, and itching (the hallmark symptom). Patients with SAC will often have few, if any, findings upon ophthalmic examination, and thus the patient's history leads to the diagnosis. Papillae—a somewhat common finding in the more-severe forms of ocular allergy—are also commonly found in children and teenagers and are not considered a hallmark for the diagnosis of SAC or PAC.

Left untreated, ocular allergies can have a negative impact on a patient's quality of life and ability to work; chronic forms can lead to ocular surface damage. Although treatment of ocular allergies can improve functionality and

from arachidonic acid by the action of cyclooxygenase and lipoxygenase, respectively. The net effect of the release of these mediators is to cause vasodilation and fluid transudation, resulting in swelling and pruritus. The acute response is often augmented by a delayed response that occurs several hours later. Although it is still regulated and initiated by IgE, the delayed response depends on upregulation of adhesion molecules and increased production of mast cells, neutrophils, eosinophils, macrophages, and basophils.¹³⁻¹⁷

From a clinical perspective, swelling and itch are the hallmark signs of an allergic response, and within the spectrum of ocular allergy, itching remains the pathognomonic symptom. This mast cell-driven inflammation caused by exposure to an ocular allergen results in transient itching, tearing, and conjunctival edema.¹⁸ Clinical examination may confirm vasodilation and reveal that chemosis is present.

As in other allergic responses, in SAC and PAC an IgE-mediated mast cell response leads to the production of histamine, leukotrienes, and prostaglandins. This initial response is rapid, generally within 30 minutes of the initial allergen exposure. During the subsequent several hours, upregulation of adhesion molecules occurs, with increased infiltration of mast cells, neutrophils, eosinophils, macrophages, and basophils into the conjunctival epithelium.¹³⁻¹⁷ The delayed phase results in additional mast cell activation within the conjunctiva, increasing the severity of the reaction.¹⁹

No one single gene has been identified as the genetic basis for allergies. Rather, the inheritance pattern of allergies implies a polygenic mode. Interleukins (ILs), especially IL-5, IL-4, IL-10, and IL-13, are the most prominent of the genes associated with allergy. IL-10 has been identified as the switch cytokine, regulating which immunoglobulin B cells will alter one isotype to another (IgM to IgG, for example). Other cytokines that can have a similar function include IL-2, tumor necrosis factor (TNF), and IL-12.

In all forms of allergic conjunctivitis, an outpouring of cytokines from conjunctival T cells can cause tearing.

These T-helper cells (both Th1 and Th2) are more prominent in AKC and VKC than in SAC or PAC. There is also some evidence of mixed helper T-cell populations in each disease type.^{20, 21} As is found in the pathogenesis of most allergic disorders, the development of ocular allergy is the result of an imbalance between Th1 and Th2 cells and their respective cytokines.¹¹ IL-4-producing T cells are the key to a switch to IgE production and also have been identified as a key component in allergic conjunctivitis.²²

Eosinophils enter the conjunctiva hours after exposure to an allergen as part of the delayed phase response and amplify the reaction by attracting lymphocytes to the site between 24 and 72 hours postexposure. These lymphocytes play a crucial role in chronic atopic disease and may initiate the formation of scar tissue. They also have been found to be more prolific in the conjunctiva of patients with more chronic disorders.

Allergy immunology models

There is a large body of literature that explores the problem of why there is a switch to production of IgE instead of IgG in patients who express allergies, including

Normal Immune Response

Raoul Wolf, M.D.

The end result of the normal immune response is the production of IgG, IgM, and IgA, which are responsible for the removal of all types of foreign antigens. IgE synthesis results from the same pathway, but unlike the other immune globulins, its only known normal function is to aid in the destruction of nematodes and other large parasites. In the absence of parasites, the usual result of IgE production is an allergic reaction.

Immune responses are initiated by a single antigen. Since the strongest immune responses depend on the three-dimensional structure of the antigen, proteins—and especially enzymes—are the most common. Epitopes, the smallest unit that can function as an antigen, are processed by an antigen-presenting cell. The main antigen-presenting cells are macrophages, but others include dendritic cells (e.g., Langerhans cells in the skin), Kupfer cells, endothelial cells, and even cerebral glial cells.

The antigen is presented to T-cell lymphocytes in the major histocompatibility complex (MHC; the identifying complex of “self”) of the macrophage. Several ILs and cytokines, especially IL-1, also communicate with T cells. In response to this stimulus, the T cells revert to blast cells and undergo rapid cell division. During this process, many more mediators and modulators are released that guide the response. At this stage, the B cell lymphocytes are triggered, and they also undergo blast cell transformation and cell division. The B cells divide into plasma cells and memory B cells. Plasma cells are antibody “factories,” producing an antibody that precisely fits the antigen. Antibodies are produced in the sequence of IgM, IgG, and finally IgA.

The immunoglobulins consist of two portions: the Fab (fragment antigen binding) end, which binds to the antigen, and the Fc portion, which binds to cells. The antibody binds to antigen in a ratio of 3:2, forming an insoluble complex and activating the complement pathway. An initial response to a novel antigen takes 10-14 days.

Suggested Reading—Immunology

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Koop E, Koop N. Anatomy and immunology of the ocular surface. *Chem Immunol Allergy* 2007;92:36-39.

Wolf RL. Function and development of the immune system in humans. In: Wolf RL, ed. *Essential Pediatric Allergy, Asthma, and Immunology*. New York, NY: McGraw-Hill; 2004: 1-20.

ocular allergies. (See “For further reading”). It seems clear that some patients have a genetic predisposition toward developing an IgE response, and these patients develop allergies. What is not clear is what acts on the predisposing genes to initiate a class switch to IgE and an allergic response. The most prominent among the paradigms is the “hygiene hypothesis.”

“Hygiene hypothesis”

Studies from Southern Germany and Sweden have shown that children who grow up on working animal farms and are exposed to animals and higher levels of endotoxin have a lower incidence of allergies and asthma than control children who grow up in the city. The interpretation of these data has led to the hypothesis surrounding development of the immune system postnatally. According to this “hygiene hypothesis” theory, the infant is born with T cells set at 0, termed Th0. Under the influence of genetics and environmental exposure, these cells become either Th1 or Th2 cells. Th2 cells are distinguished by IL-4, IL-5, and IL-13 that drive the B cells toward making IgE. It is not clear what antigens would drive Th0 cells to develop into Th2 cells, but viruses, allergens (cockroaches, dust mites, and animal dander), and reduced exposure to endotoxin have been postulated.

There are concerns about the “hygiene hypothesis” because studies supporting it do not account for the complexity of immune maturation, and this maturation probably depends on multiple factors that have yet to be delineated. In addition, most of these studies have been done in homogeneous populations and may not be applicable to the general population. Clinically, the “hygiene hypothesis” theorizes that both atopy and asthma are Th2 driven and that the imbalance between Th1 and Th2 immunity is the primary causative factor. Atopic people have increased IL-4, IL-5, IL-13, and IgE antibody responses; increased immediate skin test reactivity; and decreased interferon-gamma (Custovic A, von Mutius E. The Hygiene Hypothesis Revisited: Pros and Cons. Presented at the 60th Anniversary Meeting of the American Academy of Allergy, Asthma, and Immunology; March 7-12, 2003; Denver, CO). What role, if any, the “hygiene hypothesis” plays in ocular allergies has not been addressed.

Histamine

Histamine, a common mediator released during mast cell degranulation along with eotaxin, is stored preformed in mast cell granules. Histamine is one of the most important of the mediators and is predominant in SAC.²³ In the pure IgE-mediated mast cell response associated with SAC, histamine is the definitive cause of most of the typical signs and symptoms of ocular allergy, and, therefore, antihistamine therapy remains a prime treatment regimen.

When histamine is released into the conjunctiva, clinical responses include itching, vasodilation, and swelling. The conjunctiva hosts numerous histamine receptors; H1, H2, and H3/H4 are thought to have a role in ocular allergies. Therapeutically, H1 receptors are more predominant in

the eye; H2 is generally associated with vasodilation and nasal symptoms, although it has also been demonstrated in the blood vessels of the conjunctiva. The accumulation of fluid in the perivascular area stimulates nerve endings and causes the common “itchy” complaint. There is some evidence of H4 receptors in the conjunctiva.²⁴

The release of histamine is a controlled process. A pinocytotic vacuole forms on the outside of the mast cell, attaches to the granule, and then partially dissolves and releases a small amount of histamine. Uncontrolled or massive release of histamine causes anaphylaxis and shock and can be fatal.

Leukotrienes and prostaglandins are synthesized for each reaction by the mast cell, and thus antihistamines, leukotriene antagonists, cyclooxygenase inhibitors, and mast cell stabilizers are useful treatment modalities. The severity of ocular allergy disease correlates with the concentration of mast cells in the eye. In the late phase, the disease is mediated by eosinophils. Corticosteroids are reserved for late-phase, eosinophil-mediated conditions. Histaminases and arylsulfatase break down histamine. They are released predominantly by eosinophils and may be useful in modulating ocular allergies.

Role of IgE

During SAC and PAC the localized reaction begins with specific IgE bound to mast cells; few eosinophils or eosinophil mediators are generally present. The IgE-mediated response depends on the immunoglobulin being produced and being bound to mast cells before a clinical reaction can occur. It is thus a two-stage process: 1) exposure to the antigen causes the production of IgE specifically directed against the antigen. The specific antibody then binds to mast cells in several sites, including the conjunctiva. No reaction takes place in this phase. 2) on reexposure, the antigen binds to IgE on mast cells, causing them to disintegrate and release histamine. An allergic reaction occurs. Because of this mechanism, monoclonal anti-IgE directed against the IgE receptor is used in asthma treatment to displace IgE off the mast cells, preventing them from disintegrating and essentially rendering IgE harmless.

Prostaglandins/leukotrienes

Both prostaglandins and leukotrienes are newly formed mediators. Leukotrienes are considered more potent than histamine. LTD4 (leukotriene D4), a prominent leukotriene by-product, is considered potent at vasodilation and fluid transudation,²⁵ whereas histamine has a small effect. Prostaglandins, however, are known to induce vasodilation and are responsible for the clinical findings of redness. Both prostaglandins and leukotrienes overlap in this manner, and most targeted therapeutics are directed specifically at these mediators. Both prostaglandins and leukotrienes can be blocked by nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, and/or leukotriene modifiers. In rat conjunctiva, direct application of leukotriene B4 increased the number of eosinophils and neutrophils.²⁶

Seasonal/perennial allergies

SAC is the most common form of ocular allergy, affecting about 90% those afflicted with allergic conjunctivitis. Bilateral presentation is common, although severity may differ slightly between the eyes. Although SAC can include photophobia and blurred vision on rare occasions, it is generally not a cause of permanent visual impairment.⁵ PAC is more likely to be associated with perennial rhinitis than SAC, but otherwise the demographics of patients who have PAC versus SAC is similar. In PAC, seasonal “spikes” have been noted in up to 80% of those afflicted.⁵

Patients with PAC and SAC have elevated IgE levels in both tears and serum as well as aeroallergen sensitivity. About one-quarter of those with SAC have eosinophil infiltration in the conjunctiva but almost 80% have elevated IgE levels. Tear-fluid IgE has been reported in 96% of samples from patients with SAC.⁵ Clinically, about twice as many patients with PAC than with SAC have specific serum IgE for house dust, and the percentage of patients with SAC who test positive for IgE in tear serum is negligible. Neutrophils, basophils, and eosinophils have been found in late-phase allergic reactions.

Vernal/atopic allergies

Although patients with VKC or AKC should be closely monitored because of potential vision loss, VKC and AKC affect only a small number of patients (estimated at about 2% of those with ocular allergies). VKC has a higher prevalence in males than females; occurs more often in those who live in warmer, arid climates; and has usually run its course by early adulthood. However, in a study of 509 patients with VKC, the incidence of VKC was higher in females than males over the age of 16.¹¹ A histaminase deficiency has been reported in patients with VKC,²⁷ and intense itching, tearing, and severe photophobia are characteristic of this inflammation. Local lymphocyte phenotypes are found in patients with VKC.²⁸ During the active phase of VKC, the sheer number of cytokines (rather than the quality) will differentiate it from SAC or PAC.

AKC also occurs more frequently in men (usually between the ages of 30 and 50 years) and is associated with atopic dermatitis or atopic eczema. Typically, patients with AKC have a family history of systemic diseases (such as eczema), allergies, asthma, urticaria, or hay fever (or some combination). Atopic blepharitis, meibomian gland dysfunction, and associated dry eye symptoms commonly coexist, and the conjunctiva may be hyperemic and edematous. The periocular skin involvement can be debilitating to some patients.

Eosinophils are characteristic of both VKC and AKC. After the initial release of mast cell mediators, other cells are recruited (specifically eosinophils), which are present within hours of exposure to an allergen. Lymphocytes are

Current and future treatment modalities

When both allergic rhinitis and allergic conjunctivitis are present, comanagement with allergists, pediatricians, and eye care professionals is usually recommended. Dermatologists may also be helpful in comanaging AKC.

A stepwise approach is common when treating patients with SAC and PAC. Educating patients about the environmental allergen irritants that can be easily avoided (ie, allergens, cigarette smoke, pets) or modified (ie, keeping windows closed, cleaning ducts, replacing pillows frequently, installing hardwood floors, washing hair and pulling it back [pollen collector], and avoiding peak outdoor times when pollen counts are high) should be the first step. Although rubbing the eye may exacerbate the symptoms and perpetuate the condition, this does not have to be discussed in the first few patient visits. Cold compresses can be helpful if patients are unable to avoid the airborne allergens but do not exhibit more moderate allergy signs.

Adding over-the-counter (OTC) artificial tears (ATs) helps alleviate the itch and may also help wash away the antigen. Many SAC and PAC patients also have dry eye, and preservative-free ATs are safe to use in patients who wear CLs. ATs can provide symptomatic relief but will not address the underlying allergic response.

Antihistamines (emedastine 0.05%, levocabastine 0.05%) can provide rapid relief of ocular symptoms when applied topically. Benefits include excellent antihistamine activity plus the ability to stabilize the mast cells. Most antihistamines also inhibit eosinophil activation and migration. However, most have a limited duration of action and require up to four daily doses. CL wearers may need to discontinue use during more-severe outbreak periods. Oral antihistamines are effective in controlling some symptoms of allergic conjunctivitis but may contribute to drying of the ocular surface. Some patients benefit from the addition of topical antihistamines while they are using oral antihistamines.

Decongestants (oxymetazoline, tetrahydrozoline, and naphazoline) in combination with antihistamines act as vasoconstrictors but are known to sting or burn on instillation. Other adverse events include mydriasis and rebound hyperemia, rendering these pharmaceuticals more suitable for short-term relief. In addition, these drugs are not recommended for use in patients with narrow-angle glaucoma.³⁰ In general, vasoconstrictors should not be used to treat patients with ocular allergy because the newer antihistamines are more effective and safer.

Mast cell stabilizers (cromoglycate 2% or 4%, lodoxamide 0.1%, nedocromil 2%) can be used for long-term therapy but require a front-loading period before they can be effective. Nedocromil was more effective than cromolyn for treating VKC.³⁰

SAC and PAC are “ideally” treated with a combined antihistamine/mast cell stabilizer. Advantages of these therapeutic molecules are the rapidity of symptomatic relief coupled with the disease-modifying benefits of mast

cell stabilization. Some combination agents attack both H1 and H2. Using combination therapy allows for once-daily dosing, which increases patient compliance.

Olopatadine 0.1% was the first combined antihistamine/mast cell stabilizer to be approved in the U.S., but others include bepotastine 1.5%, epinastine 0.05%, azelastine 0.05%, pemirolast 0.1%, and ketotifen. To date, no head-to-head clinical studies comparing these combination antihistamine/mast stabilizers have been conducted. Olopatadine 0.2% is approved for once-daily administration.

Alcaftadine, “a potent histamine H1, H2, and H4 receptor antagonist that has also demonstrated anti-inflammatory properties,”³¹ is the newest antihistamine/mast cell stabilizer approved in the U.S. for allergic conjunctivitis. Alcaftadine 0.25% has a rapid onset of action and long-term duration of action.³² Alcaftadine has demonstrated an ability to inhibit eosinophil chemotaxis and activation.³³ Olopatadine 0.2% and alcaftadine 0.25% are the longest-acting antihistamine/mast cell stabilizers, allowing once-daily dosing.

NSAIDs help reduce itching in patients with allergic conjunctivitis, but to date only one (ketorolac 0.5%) has been approved for the treatment of SAC. The NSAID works on the arachidonic cascade, but the specific mode of action is unknown. Lower doses of ketorolac are currently being marketed for postoperative pain after cataract surgery but are not approved for treatment of ocular allergy. In general, nonsteroidal medications are no longer used for treating ocular allergy.

Topical steroids can be useful for VKC and AKC, but long-term use may be associated with serious adverse events, including cataract formation, glaucoma, and potentiation of herpes simplex infections. (The following statement refers to off-label or investigational use.) Off-label use of steroids via upper tarsal conjunctival injections has anecdotally shown promising results in severe VKC. Low-dose topical steroids (fluorometholone or loteprednol) are mostly recommended for patients presenting with highly inflamed eyes but should not be considered a primary long-term therapy. Systemic steroids (prednisone) can be helpful in severe cases with debilitating itching. Steroid creams have shown some benefit for patients with eyelid eczema. (The following statements refer to off-label or investigational use.) Topical pimecrolimus or tacrolimus may be used off-label on the eyelid skin. Topical cyclosporine 0.05% drops applied to the conjunctiva off-label can also provide relief as a steroid-sparing agent for patients with AKC or VKC. Matrix metalloproteinase 9 (MMP-9) activity is elevated in patients with allergic conjunctivitis and dry eye;³⁴⁻³⁶ developing therapies that specifically target MMP-9 may be warranted.

Adjunctive therapy

Allergy immunotherapy is useful in reducing the response to allergens, but its role in allergic conjunctivitis has not been proven. The therapy is administered subcutaneously in progressively increasing doses to

subsequently recruited and are believed to play a crucial role in the more-chronic disease states. Pathologic examination of the conjunctiva in these conditions will show an escalation of eosinophils being recruited. AKC patients may develop keratinized or cicatrized ocular surface similar to a pemphigoid presentation. Systemically, the true atopic individual will have extreme itch and eczematoid changes on the skin, may have developed hyperkeratosis, and is likely introducing allergens into the eye from the additional rubbing. The patient may also develop lid skin changes from using tissues to wipe the eyes for excessive tearing. The lid margin is more involved in AKC than in the other forms of allergic conjunctivitis.

GPC is caused by repeated mechanical irritation (such as occurs with contact lens [CL] use, limbal sutures, glue, scleral buckles, and prosthetic devices). It is not considered a true allergic reaction but can be aggravated substantially by allergens.

AKC and VKC can produce sight-threatening complications. The most characteristic sign of patients with tarsal VKC is giant cobblestone papillae, which are filled with eosinophils. These papillae can easily be seen by flipping the eyelids of these patients. Shield ulcers—an immunologic response to the eosinophils—can form on the conjunctiva in direct apposition to the cobblestone papillae and are generally difficult to treat, have difficulty healing, and often heal with corneal scarring and irregularities of corneal shape. In the worst cases, these ulcers can produce permanent visual loss. Limbal VKC differs not only in geographic location but in the gelatinous infiltrates that mark the limbus. People with darker pigmentation are more likely to have limbal VKC.

Patients with AKC not only have immediate allergy considerations but also have needs that should be considered when planning for future ophthalmic surgery. The chronicity of AKC can have significant implications for the health of the ocular surface, and therapy with corticosteroids increases the risk for glaucoma and cataracts. The CLEK (Collaborative Longitudinal Evaluation of Keratoconus) study did not find a strong association between keratoconus and AKC, but the increased eye rubbing has been suggested as a driving force for the progression of keratoconus.²⁹

Diagnostics

IgE levels alone may not be sufficient to determine the presence of allergy. Skin testing is more useful for demonstrating a particular sensitivity to a specific IgE. A downside to using skin tests is that they assume the mast cells on the skin are identical to those in the nose or eye, which may not be accurate. A general correlation between the environmental allergens and response is usually more accurate. Direct conjunctival sac and nasal challenges are not clinically practical but do show much higher specificity and sensitivity.

Stepwise Treatment Strategies for Allergic Conjunctivitis

Mild	Avoidance, cold compresses, tears, over-the-counter medications
	Topical antihistamines/mast cell stabilizers
	Oral antiallergics (allergists may already have patients on orals; may exacerbate the ocular condition while improving the nasal condition)
Moderate	+ Mast cell stabilizers (treats allergy before mediator is released)
	+ Combination antihistamine/mast cell stabilizers
	+ Topical corticosteroids (most beneficial for severe outbreaks)
Severe	Topical corticosteroids (short course; fluorometholone/dexamethasone/loteprednol/prednisolone)
	Topical immunomodulating agents (tacrolimus, cyclosporine)
	Oral steroids

+ = all the above, plus additional therapy as mentioned

The eye rarely stands alone—comorbidities include rhinitis, rhinosinusitis, and asthma

remain below the threshold of a clinical reaction. Immunotherapy works best in situations with severe symptoms, poor control with conventional pharmacotherapy, and good correlation of symptoms with a few specific antigens.

Sublingual immunotherapy (SLIT) is considered an alternative to subcutaneous allergy immunotherapy and is administered orally under the tongue, but long-term results with SLIT are not yet available. Most of the trials with this form of therapy have been for allergic rhinitis.

Clinical challenges in ocular allergies: case examples

On the following pages, you will find several case studies examining specific diagnostic and treatment challenges of allergic conjunctivitis. These case studies have been designed to address challenging issues that often confound allergists and eye care professionals.

Case study 1: A 30-year-old man presents during spring tree pollen season with itching and irritation of the eyes. These symptoms occur every year, but they are especially bad this year. After taking oral antihistamines, his nasal itching and rhinorrhea have decreased, but his eyes are still bothering him. He cannot play golf or mow his lawn, and he has trouble reading and using the computer at work. He tried over-the-counter antihistamine/vasoconstrictor eyedrops, but these did not provide much relief and his eyes are now redder. An eye examination reveals mild conjunctival hyperemia, trace papillae, decreased tear volume, rapid tear breakup time, and no staining.

DR. SHOVLIN: The antihistamine is probably a culprit because it reduces tear volume by 30%-40%. Before he cuts his grass, I'd advise the ad hoc usage of an antihistamine/mast cell stabilizer. I'd stop the oral antihistamine, take a closer look at the tear film, and see if we need to stabilize that in one form or another. If he's a big golfer, wrap-around glasses or sunglasses may give him some protection.

DR. LUCHS: I would approach it a little differently. This is a great case history that illustrates the real functional impact of ocular allergies on someone's daily life. If he happened to be a CL wearer, the significance of all of these factors may be elevated. The OTC antihistamine vasoconstrictor drops are not providing relief. He clearly has some signs of dry eye based on the decreased tear volume and the tear breakup time, although there is no staining. I'd keep him on the oral antihistamine because clearly he's getting some relief from his nasal symptoms and we don't want to necessarily withdraw that benefit from the patient. We need to add ATs and to treat his ocular surface. Punctal plugs won't work just yet because they could make his allergies worse by allowing us to retain antigen on the ocular surface, so we want to initiate treatment of both his allergies and dry eye before we place plugs. This is somebody that you will need to manage with preservative-free artificial tears and maybe some ointment at night; you should advise lifestyle changes and use topical antihistamines.

DR. RAIZMAN: All oral antihistamines can dry the eyes, even the so-called nonsedating oral antihistamines.

DR. WOLF: There's no reason not to stop his oral antihistamines. I would switch him to a topical nasal antihistamine.

DR. RAIZMAN: We have three different approaches here. The first is to just stop the oral antihistamines. The second is to continue the oral antihistamines but add topical ocular therapy and lubrication. The third is to stop oral antihistamines and use a nasal spray and a topical. DR. SHOVLIN: The naso-ocular lavage can help with the parasympathetic influence as a "noise cancelling" effect with allergic rhinitis. I believe just using the topical antihistamine/mast cell stabilizer would help his nasal itching as well.

DR. RAIZMAN: Some patients will describe rhinorrhea, but he also has nasal itching, which is a bit different. Pure ocular allergies do not involve nasal itch.

DR. SHOVLIN: I bet you would find therapeutically that he would do almost as well just using the topical antihistamine/mast cell stabilizer.

DR. WOLF: What tends to get lost with the non-sedating oral antihistamines is the anticholinergic effect. It depends how much the anticholinergic properties are playing a part in drying the eye as to whether these sedating antihistamines will also work. That might be a factor.

Case study 2: A 13-year-old boy with no known allergies, no rhinitis/asthma/eczema, and negative skin and RAST test results has severe ocular itching in the spring with lid swelling, red eyes, and uncontrollable rubbing. The boy has not been able to go to school for the past few days. Findings of an eye examination include lid edema and giant papillae in both eyes. The right cornea shows heavy punctate staining with fluorescein but no defect.

DR. RAIZMAN: This is a classic presentation of VKC. What are the special issues with a child with allergy as opposed to an adult in terms of drug administration, compliance, and issues with the parents?

DR. WOLF: Clinically, there are not many differences. Children need help administering the eyedrops, so parents need to take greater responsibility. It's likely this patient wouldn't initially present to an allergist. I'd recommend topical antihistamines in the eye, possibly topical therapy in addition to treating any concomitant skin involvement in blepharitis. I usually tell parents to put the drops into the inner angle of a closed eye and let the child blink to get the drop into the eye. That's usually easier. I'd refer this child, but first I'd try topical therapy, more topical antihistamines, and combination drugs. If necessary, I'd use a systemic steroid antihistamine and see him in 1-2 weeks.

DR. RAIZMAN: These kids who come in the spring need a high-dose topical steroid. I wouldn't wait 2 weeks before bringing him back. In these presentations, an immediate referral is appropriate.

DR. LUCHS: You need steroids on board right away because of the ominous corneal finding. The confluent staining of the cornea suggests that we have an area of the cornea that's ripe to become a shield ulcer. I would start the steroid right away, and I'd immediately add a topical antihistamine/mast cell stabilizer and a systemic antihistamine.

DR. SHOVLIN: Unfortunately, I hate to add additional drops, but I probably would cover him at least initially prophylactically if we're using other medications.

DR. RAIZMAN: I think that complicates things. Once the epithelial defect is there, you should absolutely use an antibiotic. Maybe an ointment would be helpful.

DR. LUCHS: Maybe even a steroid ointment at night.

DR. WOLF: From an allergist's point of view, we don't have the eye findings at that point because this child is presenting with a red eye and itching that is fairly severe. In this case, we've had a full eye exam already, which is not going to happen in an allergist's office.

DR. RAIZMAN: Let's say this is a child coming for the first time in the spring with swollen eyes and allergy. It would be absolutely appropriate to do what you said initially: Treat for a week or two. But if a child with known VKC

who has been fine for a year comes into your office in the spring, he or she should get an immediate referral and steroids.

DR. WOLF: By that point, the child is already seeing an eye care specialist. If I'm trying to control their asthma with a lot of steroids, I want someone to look in their eyes for complications.

DR. SHOVLIN: If they're on oral steroids, then the pediatrician or allergist needs to be involved. You have to find that balance. In states where optometrists can't prescribe oral steroids, they should be referred to an ophthalmologist.

Case study 3: A 44-year-old woman with known allergy to cat dander, dust, and mold presents in January with itching of both eyes and inability to tolerate her CLs. She cannot wear makeup because her eyes are tearing and she has to rub them. Her eyelashes have crust, mostly in the morning. An eye examination reveals debris on the lashes, obstructed meibomian glands, conjunctival hyperemia with minimal papillae, decreased tear volume, and punctate staining of the inferior cornea.

DR. SHOVLIN: She needs a hiatus from CL wear. She has at least a secondary dry eye (maybe from CLs or aqueous deficiency or obstructed meibomian glands), so you need to address the ocular surface as well. Before we can even think about returning her to CL wear, we have to address the lid disease and the secondary dry eye as well as the allergy. I'd start with an antihistamine/mast cell stabilizer, maybe concomitant use of ester-based steroids. This is a great patient (eventually) for daily disposable CLs.

DR. WOLF: There may be an extra wrinkle—she might have contact dermatitis that is aggravating her condition (in addition to her eye makeup).

DR. RAIZMAN: How do you decide if patients have sensitivity to their makeup?

DR. WOLF: Pattern, first of all. If there are local reactions, particularly reactions that are more on the epithelium, and if there is the initial itchiness. These are not IgE-mediated

When to refer?

Refer patient to an eye care specialist if:

- Changes in vision
- Persistent ocular complaints
- Ocular steroid use for more than 2 weeks
- Potential uveitis diagnosis
- Complaints of ocular pain

Refer patient to an allergist if:

- Systemic evaluation is warranted
- Immunotherapy is being considered
- Severe persistent allergic complaints
- Predominance of nonocular allergic complaints

Refer patient to a dermatologist if:

- Severe atopic keratoconjunctivitis and persistent contact dermatitis remain uncontrolled

reactions, so you could do patch testing or components. Nail polish is a common reactor that causes ocular reactions and local reactions because of touching.

DR. RAIZMAN: Why doesn't skin around the fingernail react but the eyelids do? I always presumed it's because the skin is so thin on the eye.

DR. WOLF: Probably the touching. Eyelids are much more sensitive. You also probably have a higher concentration of mast cells than you do around the fingernails. As makeup ages, it decays and breaks down, and the components tend to be more allergenic. I don't have a hard and steadfast rule, but using makeup that's several years old is not a good idea. I would also emphasize the removable antigens. It's highly likely she's allergic to the cat. Cat dander is very insidious, and even in homes that don't have cats there is still fine, measurable cat dander because it's brought in by visitors.

DR. RAIZMAN: The flare-up occurs in January, so this may point to cat dander or mold.

DR. LUCHS: The exam findings are consistent with blepharitis. She has lid debris, she has obstructed meibomian glands, and she has dry eye (whether it is evaporated tear loss or decreased secretion). Treat the blepharitis with warm compresses +/- lid scrubs, assuming there's no contact dermatitis; treat the meibomian gland disease with either topical azithromycin or oral doxycycline; get those functioning. And she needs to stop wearing her CLs. If allergy is a component, add a combination agent, maybe topical cyclosporine. This is a common presentation in my practice, where the primary complaint is CL intolerance. It's up to us to determine why. Is there a CL problem? Fitting issue? Hygiene issue? None of these issues would give rise to blepharitis, but they would cause her red, irritated eyes. Just because she has allergy, it doesn't necessarily mean that allergy is causing a problem, although it certainly raises it to the top of the list to something that we want to treat. I would approach this in a stepwise fashion: ask the patient to stop wearing CLs, treat the blepharitis, and support the ocular surface with artificial tears. Then see what needs to be added.

DR. SHOVLIN: This is the perfect example of where more than one issue keeps her from wearing CLs.

DR. WOLF: She probably went to her allergist when she was having these problems. From what we know from the ophthalmologic exam, she's now being seen again by her allergist. The allergist is likely to make an assumption that she's reacting to her eye makeup and not think about the CL causal factor. What I'm taking from this is that I need to begin thinking that something in the eye may be the primary cause of this patient's condition and that everything else is just aggravated by the lens wear. CL use has become as common as slipping on a pair of glasses. Allergists tend not to think about the fact you have a foreign body sitting in your eye.

DR. LUCHS: CLs can exacerbate ocular surface disease, and, conversely, ocular surface diseases can worsen CL tolerance. Dry eyes can make allergy worse. Allergy can make dry eyes worse. There's a very big interaction between all of these ocular surface diseases.

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EVALUATION

To receive CME credit for participating in this educational activity, participants must 1) review the CME information including the learning objectives and disclosure statements; 2) study the educational content of the monograph; and 3) complete the evaluation and posttest with a score of 70% or higher. Participants may retake the posttest if needed. Certificates will be sent to participants via e-mail.

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Full Name _____ E-mail _____

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- Ophthalmologist (MD/DO) Allergist (MD/DO)

I certify that I completed this CME activity. The actual amount of time I spent in this activity was (up to a maximum of 2 hours): _____ hours _____ mins

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May we contact you via e-mail regarding follow-up information or outcomes for this activity? Yes No

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Indicate the number of years you have been in practice.

- Less than 5 5-10 11-15 16-20 More than 20

Indicate your type of practice.

- Private Hospital Academic

On average, how many patients with ocular allergies do you see per week?

- Less than 5 5-10 11-15 16-20 More than 20

1. Rate the impact of the following objectives:

As a result of attending this activity, I am better able to:	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Differentiate between the various types of ocular allergies based on presentation					
Individualize management options for ocular allergy based on disease severity, patient factors, and associated risks and benefits					
Describe the newer studies on diagnostics and therapeutics that are rapidly changing potential ocular allergy treatment algorithms					

2. Rate the projected impact of this activity on your competence* and/or performance:

*Competence is defined as the ability to apply knowledge, skills, and judgment in practice (knowing how to do something).

	Yes	No	No Change
This activity increased my competence.			
This activity will improve my performance.			

3. Identify how you will change your practice as a result of attending this activity (select all that apply).

- Create/revise protocols, policies, and/or procedures This activity validated my current practice; no changes will be made
 Change the management and/or treatment of my patients Other

4. Indicate any barriers you perceive in implementing these changes.

- Cost Lack of consensus or professional guidelines
 Lack of experience Lack of resources
 Lack of opportunity (patients) Reimbursement/insurance issues
 Lack of time to assess/counsel patients Do not agree with recommendations
 Patient compliance issues No barriers
 Other, please specify _____

5. Will you attempt to address these barriers in order to change your competence and/or performance?

- N/A No Yes

6. Do you feel the activity was free of commercial bias* or influence?

*Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.

- Yes No

POSTTEST

Please circle the correct answer for each question.

1. Which condition typically includes hyperemia and chemosis?

- A. Seasonal allergic conjunctivitis D. None of the above
B. Vernal keratoconjunctivitis E. All of the above
C. Atopic keratoconjunctivitis

2. Vernal keratoconjunctivitis:

- A. Occurs more in females than males
B. Is more common in adults than children/teenagers
C. Commonly demonstrates giant papillae
D. Heavily involves the lid margin

3. Atopic keratoconjunctivitis:

- A. Is not usually associated with atopic dermatitis or atopic eczema
B. Rarely involves a family history of allergic diseases
C. Occurs more in females than males
D. Can include debilitating periocular skin involvement

4. The cell(s) most commonly involved in the early- and late-phase ocular allergic reaction is:

- A. Eosinophil C. Epithelial cells
B. Mast cell D. Endothelial cells

5. Allergic conjunctivitis is most commonly associated with:

- A. Asthma B. Urticaria
C. Allergic rhinitis D. Contact dermatitis

6. The hallmark symptom of itching in allergic conjunctivitis is primarily caused by:

- A. Tumor necrosis factor D. Histamine
B. Immunoglobulin A E. Leukotrienes
C. Eosinophils

7. Late-phase infiltration of eosinophils is most significant in which disorder?

- A. Seasonal allergic conjunctivitis D. Giant papillary conjunctivitis
B. Perennial allergic conjunctivitis E. All the above
C. Atopic keratoconjunctivitis

8. Which treatment is least often necessary for treating typical seasonal allergic conjunctivitis?

- A. Systemic steroids D. Combination antihistamine/mast cell stabilizer
B. Lubricating eye drops
C. Oral antihistamines

9. In SAC and PAC, an IgE-mediated mast cell response typically occurs within _____ minutes of the initial allergen exposure:

- A. 5 B. 30 C. 60 D. 90

10. Contact lens wearers:

- A. Should never be treated with topical lubricating drops
B. Should only be treated with topical lubricating drops
C. May have to discontinue contact lens wear during severe outbreaks
D. May have to discontinue antihistamine drops during severe outbreaks

11. What percentage of the global population has allergies?

- A. 20% C. 75%
B. 40% D. 90%

12. Shield ulcers, an immunologic response to eosinophils, are:

- A. Associated with vernal keratoconjunctivitis
B. Often difficult to treat and do not heal easily
C. Can produce permanent visual loss
D. All the above

13. One of the typical causes of perennial allergic conjunctivitis is:

- A. Dust mites C. Pollen
B. Genetic factors D. Food allergies

14. Giant papillary conjunctivitis is associated with:

- A. Bee stings C. Nut allergies
B. Contact lenses D. Aeroallergens

15. Prostaglandins and leukotrienes are synthesized from arachidonic acid by:

- A. Lipoxygenase and cyclooxygenase action, respectively
B. Cyclooxygenase and lipoxygenase action, respectively
C. Cyclooxygenase only
D. Lipoxygenase only

16. The “hygiene hypothesis” has been proven in ocular allergies. True or false?

- A. True B. False

17. _____ are a primary treatment regimen for most ocular allergies

- A. Corticosteroids C. Antihistamines
B. Topical steroids D. Immunotherapy

18. Prostaglandins and leukotrienes:

- A. Are both more potent than histamine at inducing itching
B. Are both known to increase fluid transudation into the conjunctiva
C. Cannot be blocked by NSAIDs
D. Are newly formed mediators after mast cell activation

19. Vernal keratoconjunctivitis affects a small percentage of patients with ocular allergies. True or False?

- A. True B. False

20. Artificial tears:

- A. Should not be recommended for patients with contact lenses
B. Can provide symptomatic relief
C. Address the underlying allergic response
D. Should be used only after antihistamine/mast cell stabilizers fail to provide relief.