

Special Series

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Diagnosis and management of allergic conjunctivitis

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ABSTRACT

Ocular allergy (OA), interchangeably known as allergic conjunctivitis, is a common immunological hypersensitivity disorder affecting up to 40% of the population. Ocular allergy has been increasing in frequency, with symptoms of itching, redness, and swelling that significantly impacts an individual's quality of life (QOL). Ocular allergy is an often underdiagnosed and undertreated health problem, because only 10% of patients with OA symptoms seek medical attention, whereas most patients manage with over-the-counter medications and complementary nonpharmacological remedies. The clinical course, duration, severity, and co-morbidities are varied and depend, in part, on the specific ocular tissues that are affected and on immunologic mechanism(s) involved, both local and systemic. It is frequently associated with allergic rhinitis (commonly recognized as allergic rhino conjunctivitis), and with other allergic comorbidities. The predominance of self-management increases the risk of suboptimal therapy that leads to recurrent exacerbations and the potential for development of more chronic conditions that can lead to corneal complications and interference with the visual axis. Multiple, often co-existing causes are seen, and a broad differential diagnosis for OA, increasing the difficulty of arriving at the correct diagnosis(es). Ocular allergy commonly overlaps with other anterior ocular disease disorders, including infectious disorders and dry eye syndromes. Therefore, successful management includes overcoming the challenges of underdiagnosis and even misdiagnosis by a better understanding of the subtleties of an in-depth patient history, ophthalmologic examination techniques, and diagnostic procedures, which are of paramount importance in making an accurate diagnosis of OA. Appropriate cross-referral between specialists (allergists and eyecare specialists) would maximize patient care and outcomes. This would significantly improve OA management and overcome the unmet needs in global health.

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Introduction

Ocular allergy is a common immunological inflammatory process of the anterior surface of the eye. International Consensus on Ocular Allergy was developed to provide an overview of ocular allergy (OA) and to identify unmet needs associated with the diagnosis and management of the spectrum that includes seasonal/intermittent,

perennial/persistent, vernal, and atopic keratoconjunctivitis. Ocular allergy is reported to affect up to 20% of the US population in the allergic rhinitis literature,¹ up to 40% when examined in an ophthalmological survey,^{2,3} and, like other allergic conditions, appears to be increasing.⁴ Ocular allergy has a significant impact on quality of life (QoL) as well as being an economic burden.^{2,5-9}

Diagnosis of Allergic Conjunctivitis

One of the major challenges in developing a successful strategy in the care of patients with OA is that OA is often self-diagnosed, underdiagnosed, or misdiagnosed by health professionals. Most

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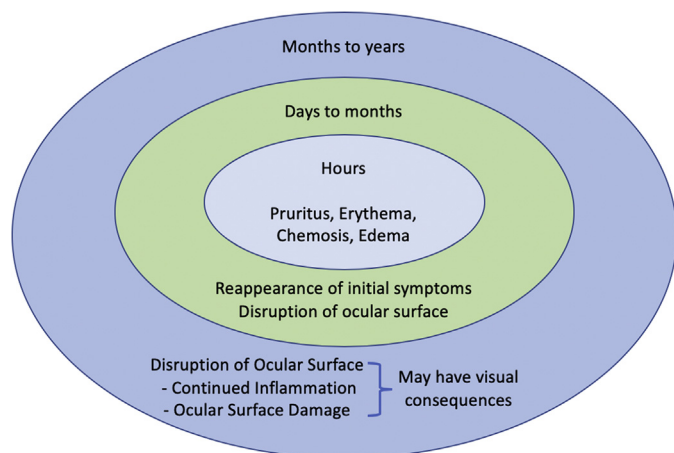


Figure 1. Untreated or undertreated ocular allergy. (A) Progressive effects of ocular allergy: From the immediate acute exposure to allergen leading to the acute phase with itching, swelling, and redness to persistent symptoms that can eventually disrupt the ocular surface from the toxic metabolites of eosinophils and other mediators

patients self-diagnose their ocular symptoms and resort to over-the-counter use of medications.^{10,11} Ocular allergy is most commonly diagnosed and managed by the general practitioner (internist, pediatrician, family physician), but it is often undertreated. Studies have noted that anterior ocular surface diseases (eg, OA, infections, blepharitis, and dry eyes) are prone to misidentification in the primary care setting, leading to inappropriate treatment.¹² Ocular allergy was reported in a UK study as the diagnosis for 13% of “eye problems” in general practice, further supporting the fact that most patients with OA are seen in the general practitioner’s office, as noted in a recent US study; these patients are rarely referred to specialists for assessment, even though they may present with other signs and symptoms of a more systemic allergic disorder^{6–13} (Fig 1). When the patient is nonresponsive to first-line therapeutic interventions, or in patients who developed a more complex and potentially sight-threatening anterior surface ocular disorder, specialist assistance is necessary (specialists include allergists, immunologists, and ophthalmologists)^{1,14,15} (Fig 2). In specialty practice, evaluation of ocular allergy should include focused history, appropriate diagnostic tests (eg, immunoglobulin E [IgE] tests, patch test, Schirmer’s test), and markers of inflammation (eg, tear osmolality, tear matrix metalloproteinases) to assist in appropriate prescription of advanced therapies, including immunomodulatory agents and allergen immunotherapy⁶ (Table 1).

History

The red eye is a common sign that many consider the hallmark of all forms of conjunctivitis, although it also may be present from involvement of other structures of the eye other than the conjunctiva (eg, scleritis, uveitis, and acute glaucoma; Fig 3).

Ocular itching and blurring of vision are the most prevalent symptoms of ocular allergy. These symptoms often occur simultaneously with nasal symptoms (Fig 4). At one point, ocular symptoms were thought to be secondary to nasal provocation; however, we know both ocular and nasal symptoms can be separately induced. Although the threshold point for evoking nasal symptoms has been found to be on average lower than the threshold point for evoking ocular symptoms, the severity of ocular symptoms of “red, itchy eyes” when compared with the most common complaint of “nasal congestion” have not been found to be statistically different.²

Of note, pain and photophobia are more related to chronic ocular allergic disorders caused by loss of epithelial integrity of the cornea.

Physical Examination

The initial examination begins with the naked eye, using a light source such as a penlight or ophthalmoscope for illumination. The ophthalmoscope also offers the advantage of being a source of magnification and illumination with a *magnification* of approximately 15× and a field of view up to 10 degrees. The slit lamp (biomicroscope) examination used by ophthalmologists and optometrists offers the widest range of examination up to a magnification of 16×.

Other rare causes of a “pink” or “red” eye include increased intraocular pressure. The gross measurement of intraocular pressure can be performed by palpating the eye through a patient’s closed lids and may assist in determining extremely low or high pressures, either of which are signs of potentially serious ocular pathologic conditions. A normal eye can be slightly indented on direct palpation, whereas a “pink eye” with acute angle closure is hard and frequently cannot be indented. Unfortunately, most cases of high intraocular pressure are asymptomatic and difficult to detect without the use of a tonometer. If there is a concern of high intraocular pressure, a referral to an eye care specialist is warranted.

Papillae may be seen in the conjunctiva of the ocular surface at the superior limbus of the eye (ie, the junction between the cornea and sclera), leading to cobblestoning and limbal lesions known as Horner-Trantas’ (or Trantas’) dots containing eosinophils (Fig 5). Trantas’ dots are most commonly associated with the more chronic forms of ocular allergy (eg, vernal keratoconjunctivitis and atopic keratoconjunctivitis). Stringy mucus threads are a common feature of chronic forms of conjunctivitis.

General Classification of Inflammatory Disorders of the Conjunctiva

The nosology of OA includes seasonal and perennial, in which the condition affects the ocular surface for the duration of allergen exposure; *seasonal* based on phenology of the specific aeroallergen, and *perennial* because of the ongoing presence of an allergen such as house dust or pet dander. Because the terms *seasonal* and *perennial* do not include specific duration, international consensus panels have suggested the terms of intermittent (<4 weeks in duration) or persistent (>4 weeks). One of the chief difficulties distinguishing between acute and chronic forms of OA is determining the role of specific triggers. Chronic allergic conditions appear to represent a spectrum of anterior ocular surface diseases caused by either a persistent allergen stimulus or a progression of the immune response irrespective of the specific allergenic trigger (Fig 6).

Pharmacoeconomics

Underdiagnosed and undertreated ocular symptoms associated with allergic rhinitis are recognized as imposing a substantial burden of disease reflected in poor health-related QoL and a high economic impact for allergy patients. The global ophthalmic medication market is constantly evolving, with 40% of the market in the 1990s dedicated to anti-infectives, and now appears to be almost equally distributed between anterior ocular inflammatory diseases, including OA (25%), infection (30%), inflammation (14%), and dry eye (31%), with prescription drug expenditure approaching approximately \$7 billion US annually.¹⁶ In the United States, the prevalence of nasal and ocular symptoms have more than doubled since the mid 1970s.³ The economic impact of OA is estimated to be over \$2 billion US annually in prescriptions generated by primary care physicians (30%), eye

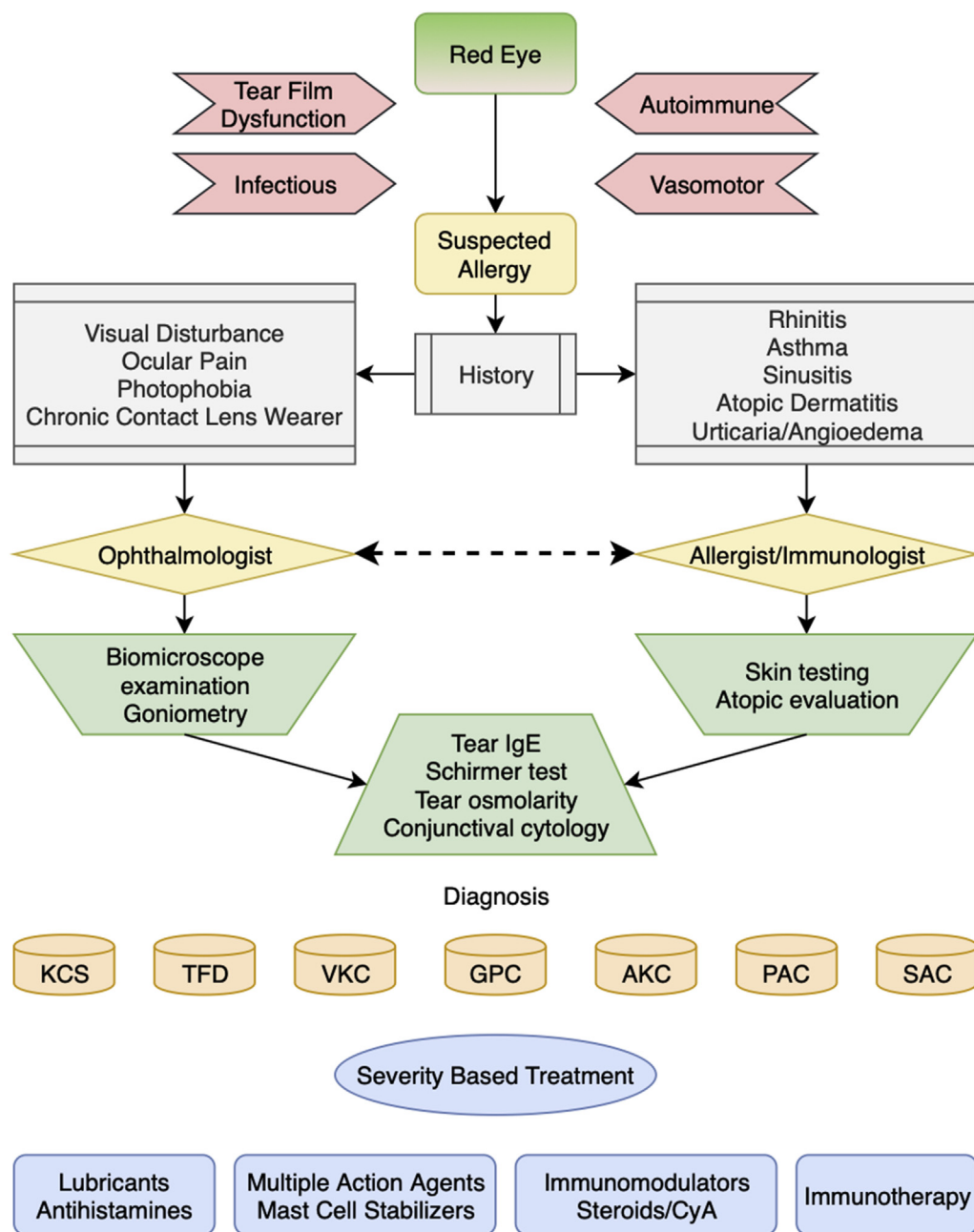


Figure 2. Allergist and eye care specialists: multidisciplinary approach.

care specialists (41%), and allergists (9%) This excludes over-the-counter medications projected to be 10-fold more than prescription sales.¹⁶ Cost also includes indirect expenses (QoL reduction, out-of-pocket expenses, self-perception, work/school absenteeism) and direct (insurance and health care systems) financial burden. In the original allergic rhinitis QoL instrument, symptoms in the ocular domain in patients with rhinitis had the

largest impact.¹⁷ In a cross-sectional study in Portugal, patients who self-treated their OA had serious reduction in QoL.⁵

Immunopathophysiology

The ocular surface is an immunologically active one, because it is in constant contact with the environment and is distinct from the

Table 1
Misdiagnosis—Warning Signs for Sight-Threatening Conditions

• Decrease in visual acuity • Ciliary flush: A pattern of injection in which the redness is most pronounced in a ring at the limbus (the transition zone between the cornea and the sclera) that would signify concern for infectious keratitis, iritis, angle closure glaucoma • Photophobia • Severe foreign body sensation that prevents the patient from keeping the eye open • Corneal opacity • Fixed pupil • Severe headache with nausea

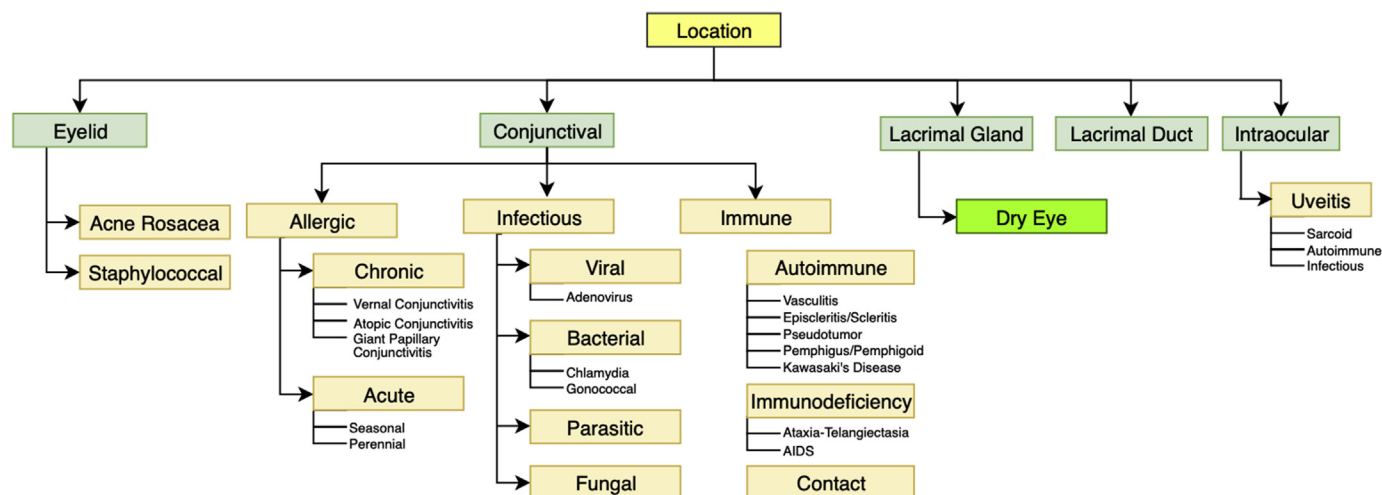


Figure 3. The differential diagnosis of the red eye. (A) The differential diagnosis of ocular allergic disorders includes a variety of other causes, including allergic, infectious, autoimmune, and mechanical or nonspecific that activate the hypersensitivity responses of the extraocular and intraocular immunologically active tissues. These include acute and chronic allergic conditions (eg, giant papillary conjunctivitis, vernal conjunctivitis, atopic keratoconjunctivitis, superior limbic conjunctivitis, follicular conjunctivitis); infectious causes (eg, chlamydial disease, molluscum contagiosum, Parinaud's oculoglandular syndrome); and miscellaneous disorders including keratoconjunctivitis sicca, acne rosacea, ocular pemphigoid and blepharoconjunctivitis.

internal portions of the eye that are immuno-privileged. Ocular allergy has been defined as an anterior ocular surface inflammatory disorder mediated primarily by triggering the IgE-mast cell system.¹⁸

Histamine from degranulated mast cells binds receptors (H1, H2, H3, and H4) on vascular endothelial cells, neuronal fibers, goblet cells, immune cells, and conjunctival epithelium, culminating in the clinical manifestations of allergic conjunctivitis; these include rubor (redness, erythema),¹⁹ tumor (periocular swelling, chemosis), dolor (itching, pruritus), and tearing. Selective agents binding these receptors offer the possibility of different therapeutic effects.²⁰ Histamine receptor subtype agonists, as part of a therapeutic paradigm, impact the various components of allergic inflammation, including altered permeability of conjunctival epithelium leading to epithelial barrier disruption; stimulation and release of adhesion molecules, chemokines, and pro-inflammatory cytokines; and recruitment and activation of dendritic cells leading to maturation of antigen-presenting cells and activation of CD4 Th2-lymphocytes.

The CD4 Th2 lymphocytes, in conjunction with mast cells, are the major immune cells involved in acute, but more importantly, in the chronic allergic inflammatory responses of the ocular surface. In the more chronic forms of allergic conjunctivitis, such as vernal keratoconjunctivitis (VKC) in children and atopic

keratoconjunctivitis (AKC) in adults, the following changes are evident: a persistent state of mast cell, eosinophil, and lymphocyte activation; noted switching from connective-tissue to mucosal-type mast cells; increased corneal pathology; and follicular development and fibrosis (remodeling of the ocular surface environment).

Disruption of tight junctions between epithelial cells appears to be the defect that allows increased allergen exposure and binding of specific IgE molecules and ultimately mast cell activation in the substantia propria.²¹ Tryptase, released after mast cell activation, leads to induction of conjunctival fibroblasts.

Mediators released during the late phase of allergic inflammation of the ocular surface have been targets of therapeutic interventions. These have included lipid mediators (prostaglandins and leukotrienes) formed from the mast cell membrane arachidonic acids by oxidative metabolism and a number of cytokines that specifically recruit and activate eosinophils, lymphocytes, monocytes, and neutrophils. Cytokines released from local conjunctival epithelial cells and fibroblasts also have been implicated in the more chronic forms of allergic conjunctivitis (AKC, VKC, giant papillary conjunctivitis [GPC]); they perpetuate the persistent infiltration of lymphocytes, eosinophils, and neutrophils onto the ocular surface and can lead to serious visual axis impairment²² (Table 2).

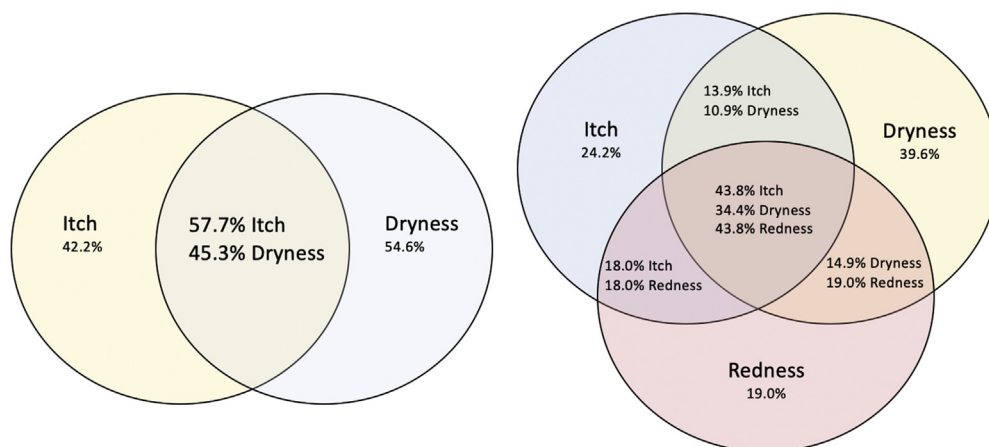


Figure 4. Symptom overlap in ocular allergy patients. (A) (From Hom MM, Nguyen AL, Bielory L. Allergic conjunctivitis and dry eye syndrome. *Ann Allergy Asthma Immunol*. 2012; 108[3]:163-166.)

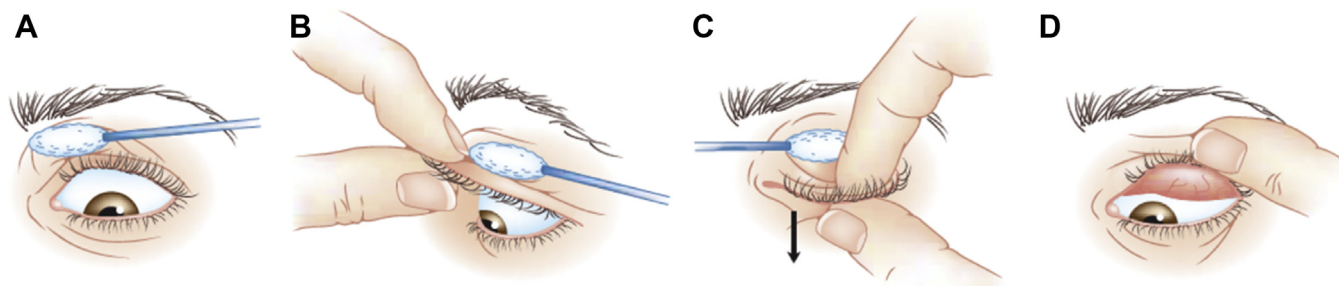


Figure 5. Technique demonstrating the eversion of the upper eyelid. (A) Examination of the conjunctiva. The technique for evaluation of the bulbar and palpebral portion of the upper and lower conjunctiva requires the eversion of both lower lids and then the eversion of both upper lids. The eversion of the upper lid is performed by the placement of a cotton-tipped swab above the eyelid (A) and then, while the patient is asked to look downward, the upper eyelash is gently grasped (B). The upper eyelid is gently pulled down while placing pressure on the upper portion of the eyelid with the cotton swab (C), and then it is lifted over the surface of the swab (D). This procedure is helpful when looking for papillary and follicular development in patients with more chronic forms of conjunctivitis.

Evaluation and Diagnostic Studies for Seasonal/Intermittent and Perennial/Persistent Allergic Conjunctivitis

Allergy tests should be considered to provide evidence of an allergic basis for the patient's symptoms, to confirm suspected causes of the patient's symptoms, or to assess the sensitivity to a specific allergen for avoidance measures or allergen immunotherapy.²³

Skin Prick Test

Epicutaneous tests ("prick," intradermal) (SPT) remain the most simple, rapid, and inexpensive procedure for the diagnosis of allergen sensitivity in patients with ocular allergy. Skin tests provide evidence of specific sensitivity to external environmental allergens within 20 minutes after placement on the skin. A positive wheal-and-flare reaction reinforces the concept of specific

allergen sensitization to the patient. The test is highly sensitive for systemic allergies, such as allergic rhinitis and allergic asthma, but it does not always correlate with allergic sensitization of the ocular surface. The skin test remains a confirmatory test that may, in unusual circumstances, require use of additional in vivo local tests such as a conjunctival provocation test to confirm specific allergen sensitivity of the ocular surface.²⁴ Serum-specific IgE measurements should be considered when SPTs are discordant with the medical history or contraindicated, or as an alternative to SPT to quantify allergen specific IgE to native or purified components.¹⁴

Patch Test

The presence of eczematous blepharitis or blepharoconjunctivitis may suggest the possibility of a delayed-type

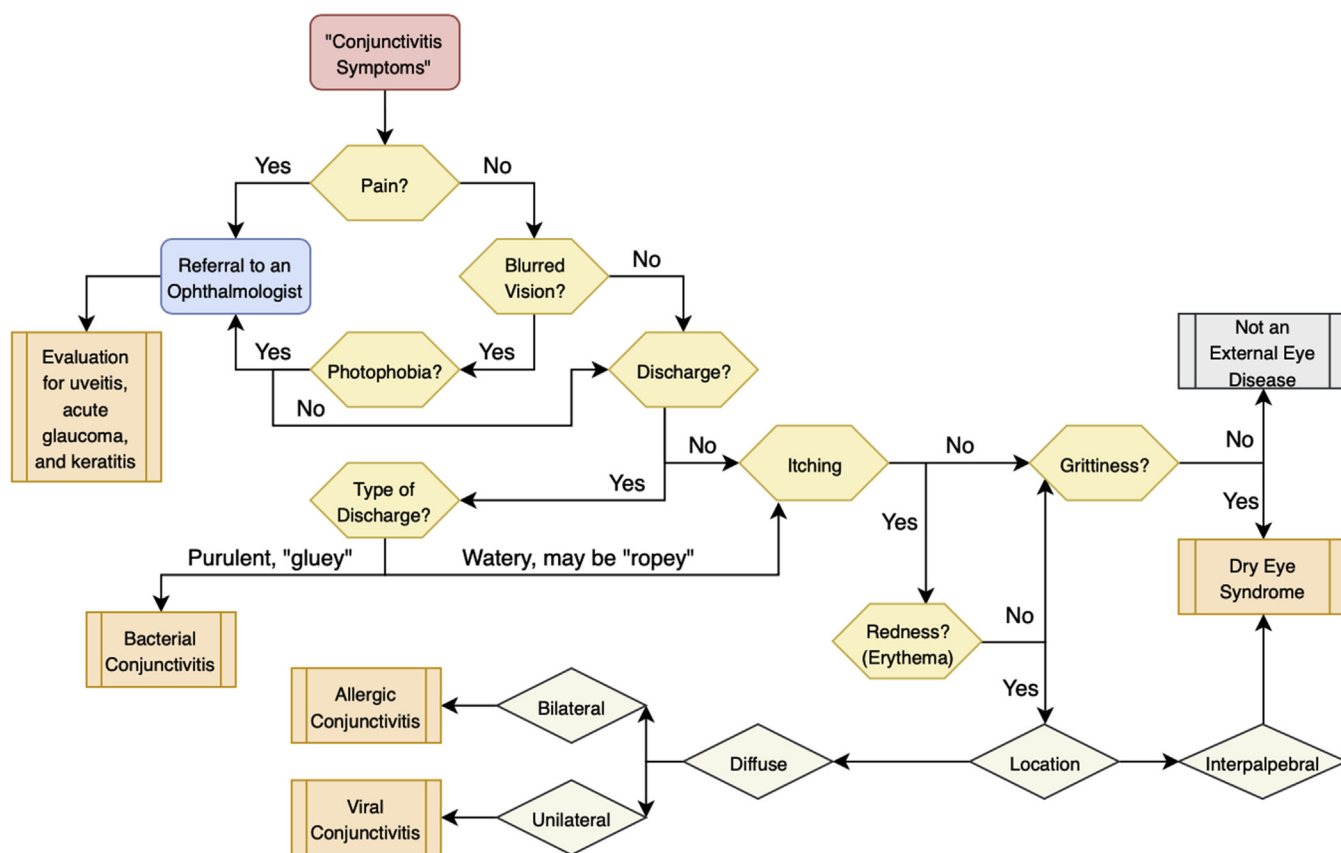


Figure 6. Differential diagnosis: signs and symptoms.

Table 2
Immunopathophysiology—Summary Statements

- The symptoms of allergic conjunctivitis result from a complex allergen-driven mucosal inflammation resulting from interplay between resident and infiltrating inflammatory cells, a number of vasoactive and pro-inflammatory mediators including cytokines and neuropeptides.
- An IgE response to seasonal or perennial allergens is the most common pathophysiologic mechanism of ocular allergy.
- The ocular response to specific allergen challenge is characterized by an early- and late-phase reaction.
- Eosinophilia is a relevant cytologic hallmark of allergic conjunctivitis.
- Involvement of different immune cell populations (mast cells, eosinophils, and lymphocytes) may cause more severe symptoms that can threaten the cornea and vision in the more chronic forms of ocular allergy.

reaction, and patch testing may be necessary to delineate the specific antigen. This involves applying a series of potential chemical sensitizers in aluminum or cellulose disks to the skin of the back; these are removed after 48 hours and the patches examined at multiple time points. Benzalkonium chloride and thimerosal, preservatives present in ophthalmic and contact lens solutions, are common culprits.²⁵ Thimerosal is an organomercurial derivative of thiosalicylic acid. It has been used as a disinfectant that acts by combining with the sulfhydryl groups of proteins to precipitate bacterial proteins by forming proteinates of mercury (eg, merthiolate). The proteinates act as neoantigens that cause the highest frequency of cell-mediated responses of all the ophthalmic preservatives. It is most commonly found in soft contact lens solutions and may cause ocular delayed hypersensitivity.

If topical agents are suspected, patch tests can be performed by using the exact solution in question. Periorbital skin is quite different from other sites such as that of the back, not only for the depth of epithelial and dermal layers, but also for the limited number of mast cells present and for its limited exposure to the external environment compared with the eyelid. For example, possibly sun exposure exacerbates specific and nonspecific hyper-reactivity reactions only on the lid skin.

Conjunctival Provocation Test or Conjunctival Allergen Challenge

Conjunctival Provocation Test (CPT) or Conjunctival Allergen Challenge (CAC) can be likened to “skin testing” of the eye, because known quantities of specific allergen are instilled onto the ocular surface, and the resulting allergic response is measured at 15 to 30 minutes, similar to skin testing. Mediator release and cellular infiltration are relatively easily measured in tear samples. This technique is primarily used in the assessment of new drugs for ocular allergies, but it can sometimes be used to define suspected sensitizing allergens that appear to be limited to the ocular surface.^{26,27} The immediate positive response is characterized by the same signs (redness, chemosis, and lid swelling) and symptoms (itching and tearing) as those the patients experience after natural exposure to the antigen. The positive reaction usually subsides gradually, within 20 minutes. A late-phase inflammatory reaction also may occur, depending on allergen dose and patient sensitivity. The CPT is a safe and simple procedure that provides valuable clinical information with limited systemic side effects (generalized itching, bronchospasm, anaphylaxis) that are rarely seen.²⁸

Nonspecific Provocation Test

Ocular challenge with histamine or hyperosmolar solutions has been used to verify a nonspecific hyperresponsiveness of the conjunctiva in allergic patients.²⁹ Vernal keratoconjunctivitis patients were shown to respond with lower concentrations of histamine, although this remains experimental at this point.³⁰

Tear Film Evaluations

Measurement of total IgE in tears

Normal values of IgE in tears are normally very low, less than 2.5 kUI/L (3 ng/mL), because of the blood–tear barrier. Detectable tear IgE levels indicate local production of antibodies and suggest a diagnosis of allergic conjunctivitis.

Tear osmolarity

Tear osmolarity should be evaluated for supporting the diagnosis of tear film dysfunction (previously known as dry eye syndrome).^{31,32} Hyperosmolarity suggests a form of dry eye.

Schirmer test

The Schirmer tear test is the most commonly used and easily performed test for tear production by the lacrimal gland in the evaluation of dry eye. The Schirmer I test (without anesthesia) measures both basal and reflex tearing (abnormal, ≤ 5 mm of wetting after 5 minutes). The Schirmer II test (with anesthesia) measures only the basal secretion of tearing (abnormal, ≤ 3 mm of wetting after a 5-minute interval).

Ocular Surface Staining Procedures

Fluorescein

Fluorescein is a water-soluble dye used to examine the cornea, conjunctiva, and the precorneal tear film by staining denuded areas of corneal epithelium and pooling into surface irregularities. Under a cobalt blue filter, the fluorescein dye produces a blue hue against an intense green color. The newer slit lamps feature a yellow filter in addition to the cobalt blue filter to enhance viewing. Most eye care practitioners prefer to use the additional yellow filter because it makes the staining much easier to see. Soft contact lenses must be removed before fluorescein instillation to prevent permanent lens staining. They can be reinserted after an hour. Fluorescein staining is the standard clinical diagnostic test to detect the presence of corneal epithelial surface defects seen in chronic forms of ocular allergy.

Rose Bengal

Rose Bengal is a red dye derivative of fluorescein, does not stain the precorneal tear film, and stains only dead and degenerating (not denuded) epithelium of the conjunctiva and cornea. It also stains mucous particles, strands, filaments, and plaques more vividly than does fluorescein, making it a better diagnostic aid in the evaluation of the conjunctiva and tear film. However, it is rarely used because of sensory irritation (stinging).

Lissamine green

Lissamine green dye fades relatively quickly, is less irritating than Rose Bengal staining, and is used both clinically and in drug studies. The stain usually requires a wait period between 1 and 2 minutes after instillation for optimal viewing.

Conjunctival Cytodiagnosis

Evaluation of the number and percentage of leukocytes on the ocular surface in the active phase of conjunctival inflammation can be essential to the decision of how to proceed with further diagnostic tests. The presence of even 1 eosinophil is highly indicative of an allergic pathology, whereas their absence does not exclude an allergic diagnosis. Conjunctival scrapings are performed with a spatula; this allows for the collection of more cells than performance of tear cytology, which is performed on a sample collected by a glass capillary from the external canthus. Both samples are examined on a slide. Impression cytology using nitrocellulose

Table 3
Diagnostic Testing—Summary Statements

- Skin tests represent the primary allergy test for diagnosis of sensitization in patients with ocular allergy.
- Immunoassays for IgE determination represent secondary allergy test for diagnosis of sensitization in patients with ocular allergy.
- Conjunctival provocation testing (CPT) with the sensitizing allergen may be useful for evaluating the ocular inhibitory effects of anti-allergic agents and for research purposes.
- Conjunctival cytology is an additional useful tool for diagnosis of allergic conjunctivitis.

membranes is mostly used for tear film pathology, because it is a nontraumatic means to evaluate the morphology of the superficial conjunctival epithelium by either light or electron microscopy. Emerging technologies include meniscometry, optical coherence tomography, tear film stability analysis, interferometry, tear osmolarity, the tear film normalization test, ocular surface thermography, and tear biomarkers.³³ Impression cytology, a technique for harvesting cells from the superficial bulbar conjunctival surface, is a quick and painless tool to assess a considerable assortment of inflammatory biomarkers (Table 3).³⁴

Comorbid Conditions

Allergic conjunctivitis is commonly a local manifestation of the systemic allergic condition, with more than 95% of patients with seasonal or perennial allergic conjunctivitis having allergic rhinitis,³⁵ justifying the past use of “allergic rhino-conjunctivitis” as a synonym of this disease. However, with the arrival of ICD-10, allergic conjunctivitis has been listed as a separate diagnosis. Allergic rhino-conjunctivitis is associated with allergic airway disorders (sinusitis, asthma, otitis media) that share common immunopathogenic mechanisms.^{36–48} Twenty-three percent of children with allergic rhino-conjunctivitis have secretory otitis media, whereas the prevalence of allergic rhino-conjunctivitis in children with otitis media and Eustachian tube dysfunction ranges from 22% to 50%.^{35,40,47,49} Twenty-nine percent of patients with nasal polyps have allergic rhino-conjunctivitis.⁴⁶ Seventeen percent to 21% of patients with allergic rhino-conjunctivitis have asthma, and 28% to 80% of patients with asthma have allergic rhino-conjunctivitis.^{35,36,39,40,42,45,47,50} Dry eye is a frequent comorbidity (approaching 50%) of patients with ocular allergic disease.⁵¹ These data strongly suggest the importance of a multidisciplinary approach to the allergic conjunctivitis patients, with the involvement of the allergist, pediatrician, internist, family medicine, otolaryngologist, and eye care specialists.

Ocular symptoms associated with allergic rhinitis are recognized as imposing a substantial burden of disease—health-related

Table 4
Allergic Conjunctivitis—Key Concepts

- Conjunctivitis caused by IgE-mast cell–mediated reactions are the most common hypersensitivity responses of the eye.
- Seasonal allergic conjunctivitis is the most common form of allergic conjunctivitis, representing more than half of all cases.
- Grass pollen, dust mites, and animal dander are the most common allergens.
- Most environmental allergens affect both eyes at once.
- The hallmark of allergic conjunctivitis is pruritus.
- A stringy or ropy discharge also may be characteristic of allergy.
- A detailed history is the cornerstone to proper diagnosis.
- Eye examination: simple observation alone may be diagnostic.
- Ocular inflammation caused by systemic immunologic diseases are frequently observed in children.
- Immunologic disorders of the eye commonly affect the interior portion of the visual tract and are associated with visual disturbances.

quality of life and economic impact on allergy patients. The involvement of the eyelid, such as in contact dermatitis and blepharitis, is a common finding in chronic forms of OA (eg, AKC). Periocular skin becomes scaly and flaky, and the lids may eventually become thickened. High prevalence of allergic diseases of the upper and lower airway has also been described in VKC and AKC.⁵² Skin eczema or dermatitis is a common feature in AKC, confirming that this ocular disease is the local manifestation of the atopic eczema/dermatitis syndrome. More than 65% of patients with active atopic dermatitis show the coexistence of AKC (Table 4).⁵³

Chronic Ocular Allergic Conditions

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a seasonally recurrent disease state with an increase in mast cells, eosinophils, and lymphocytes. It represents a hypersensitivity reaction that has overlapping features of IgE sensitization and mast cell activation that evolves to be a chronic inflammatory lymphocyte-predominant condition. *Vernal* refers to the frequent spring-time onset and exacerbations of VKC. Eosinophils appear to be important in the pathogenesis of VKC, because degranulated eosinophils and their toxic products (eg, major basic protein) are found in the conjunctiva and in the periphery of corneal ulcers in severe forms of VKC. The condition has an increased prevalence in children and in the countries surrounding the Mediterranean basin.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis is associated with continuous contact between the conjunctiva of the upper eyelid and a foreign body such as an ocular prosthesis, exposed suture, or more commonly, contact lenses. The papillary conjunctival response is a clinical inflammatory sign of fine (<1 mm), elevated, polygonal, hyperemic areas that can be seen in a mosaic covering of the upper and lower eyelid conjunctiva. Papillae are usually restricted by fibrous connective tissue septae in the palpebral (lid) conjunctiva that appear as pale channels. With disruption of the fibrous septae, giant papillae (>1 mm) develop. Unlike a fine papillary response, which is a nonspecific finding, progression to giant papillae appears to be related to allergic or other hypersensitivity reactions. “Cobblestoning” refers to enlarged papillae with a hard, flat-topped, polygonal appearance. In addition to GPC, giant papillae may be seen in VKC and AKC.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is a chronic inflammatory condition that involves a mixture of mast cell, IgE, and lymphocytic interactions generating infiltrations of eosinophils, plasma cells, and lymphocytes in the conjunctiva. It typically occurs in the adult population with atopic comorbidities, especially eczema and asthma.

Contact Dermatitis

Contact dermatitis is a cell-mediated delayed-type hypersensitivity reaction causing a blepharoconjunctivitis that is frequently confused with an acute intense mast cell/IgE-mediated allergic conjunctival reaction. Eyelid involvement generates significant swelling, and redness can occur despite only minor degrees of inflammation because of its thin and pliable surface. Contact dermatitis involving the eyelids most frequently is caused by cosmetics applied to the face, hair, or fingernails rather than to the eye area directly.

Table 5
Diagnosis—Summary Statements

- Allergic conjunctivitis is not a single disease and is not exclusive of conditions such as tear film dysfunction.
- Seasonal and perennial allergic conjunctivitis are the most common allergic disorders.
- An accurate clinical history and evaluation of signs and symptoms allow the diagnosis of ocular allergy and the definition of possible sensitizing antigens.
- IgE-mediated hypersensitivity and mast cell degranulation are the initial pathophysiological mechanisms.
- Identification of specific sensitizing allergens is useful for avoidance.
- Prick test is the primary recommended allergy test.
- Allergic conjunctivitis may occur in patients' skin/prick test and serum specific IgE negative.
- The cornea may be involved in vernal keratoconjunctivitis, atopic keratoconjunctivitis, or contact blepharoconjunctivitis but not in seasonal nor perennial allergic conjunctivitis.
- Cytological tests are useful in the active phase of the disease.
- Conjunctival allergen provocation can prove local hypersensitivity.

Table 6
Allergic Conjunctivitis—Therapeutic Principles

- Therapy is to be approached in a stepwise fashion:
- Primary: Avoidance, cold compresses, and artificial tears
 - Secondary: Topical antihistamines, decongestants, mast cell stabilizers, nonsteroidal anti-inflammatory drugs, or multiple action agents
 - Tertiary: Topical corticosteroids or immunotherapy (immunotherapy may be considered in the secondary category for some cases)
 - Novel approaches^a: cyclosporine, tacrolimus, liposomal drug delivery systems, cytokine antagonists, anti-IgE therapy, complementary and alternative medicine.
 - Ophthalmology or optometry consultation is merited for any persistent ocular complaint or if the use of strong topical steroids or systemic steroids is being considered.

^aNone of these is approved for the treatment of ocular allergy by regulatory agencies.

the pediatric population, but secondary bacterial infection with sinus involvement may be a complication. Symptoms of acute infectious conjunctivitis include hyperemia, irritation, tearing, mucopurulent exudate, and matting of the lids. It may begin as a unilateral condition.

Occupational Conjunctivitis

Occupational conjunctivitis refers to ocular symptoms arising in response to airborne substances in the workplace, which may be mediated by allergic or nonallergic factors, such as laboratory animal antigen,^{61,62} grain,^{63–65} organic chemicals,^{66–70} and irritants.^{71–74} Case reports also have described occupational conjunctivitis to wool,⁷⁵ plants,^{76–79} coconut fiber dust,⁸⁰ fish parasite,⁸¹ detergent protease,⁸² and white pepper.⁸³ It often coexists with occupational rhinitis and asthma.

Drug-Induced Conjunctivitis

Drug-induced allergic conjunctivitis can occur as a reaction to long-term use of topical ocular therapies (eye drops, ointments, contact lens solutions, etc.) and is often caused by an adverse reaction to chemical preservatives in the ophthalmic solutions.^{14,84–88} Drug-induced conjunctivitis may be caused by a number of medications, including pamidronate,^{89,90} erectile dysfunction agents,⁹¹ cytosine,⁹² and herbal medications.⁹³ The topical induced reactions often occur in the lower eyelid and inferior conjunctiva, because liquid therapeutics tend to pool in these areas. Patients usually present with red-colored inflamed conjunctiva, papillae development, pinpoint keratitis, and chemosis.⁹⁴ A specific form of drug-induced conjunctivitis that parallels the occurrence in the nose is conjunctivitis medicamentosa, which is the increased conjunctival injection and rebound hyperemia following the overuse of vasoconstricting eye drops.⁹⁵

Misdiagnosis

Pink eye “conjunctivitis” is commonly assumed to be bacterial and is overprescribed with antibiotics. To provide the correct diagnosis, the clinician needs to review the history, symptoms, and signs before treating. There may be a corneal or conjunctival foreign body or traumatic iritis in a patient with a recent history of trauma. Sight-threatening conditions that can mimic the “pink eye” of allergic conjunctivitis include infectious keratitis, iritis, and acute angle closure glaucoma (Table 5).

Treatment (Step Approach)

In some patients, management commonly starts with self-treatment or the use of over-the-counter regimens with pharmacy input.^{96–98} Discordance in approach between primary care physicians and eye care specialists also has been shown.¹³ Although the diagnosis of most ophthalmic diseases seen in general practice can

Nonallergic Conjunctivitis Syndromes

Some nonallergic, noninfectious syndromes are attributable to other forms of inflammatory activation that mimic ocular allergy. The autoinflammatory diseases, also termed periodic fever syndromes, may present with ocular hyperemia.

Dry Eye Disease (Tear Film Dysfunction)

Dry eye is a frequent comorbidity of ocular allergic disease. It is sometimes difficult to correctly differentiate between patients with dry eye and those with more serious pathologic conditions, including ocular allergy.⁵¹ True dry eye develops from decreased tear production, increased tear evaporation, or an abnormality in specific components of the aqueous, lipid, or mucin layers that constitute the tear film. Although dry eye may result from intrinsic tear pathology, it is frequently associated with other ocular disorders and systemic diseases, including ocular allergy, chronic blepharitis, fifth or seventh nerve palsies, collagen vascular disease, hormonal changes in women, Sjögren syndrome, vitamin A deficiency, pemphigoid, and trauma. Dry eye is also associated with many pharmacologic agents, including antihistamines, anticholinergics, and some psychotropics. Symptoms of dry eye are typically vague and include foreign body sensation, easily fatigued eyes, dryness, burning, ocular pain, photophobia, and blurry vision.⁵¹ Symptoms tend to be worse late in the day, after prolonged use of the eyes or exposure to environmental conditions.

Nonallergic Perennial (Vasomotor) Conjunctivitis

Vasomotor conjunctivitis is a perennial, chronic form that comprises a heterogeneous group of chronic ocular symptoms that are not immunologic or infectious in origin and are not associated with ocular eosinophilia.⁵⁴ It is commonly seen in the elderly and is thought to be influenced by age-related physiologic changes, such as anatomic and mechanical changes.^{55,56} It also can be seen in the athletic population exposed to chlorinated swimming pools. Appropriate management of symptoms with safe, effective, and permitted medications needs to be addressed to not compromise the athlete's performance ability or interfere with their ability to compete.^{57–61} In addition, tear film dysfunction should be considered high in this population. Common complaints include excessive tearing from exposure to cigarette smoke, fumes, and perfumes, resulting in varying degrees of intensity of conjunctival injection.

Infectious Conjunctivitis

Infectious conjunctivitis may be acute or chronic, depending on the infectious agent. Viruses are more commonly associated with acute conjunctivitis (~98%) with most conjunctivitis symptoms in

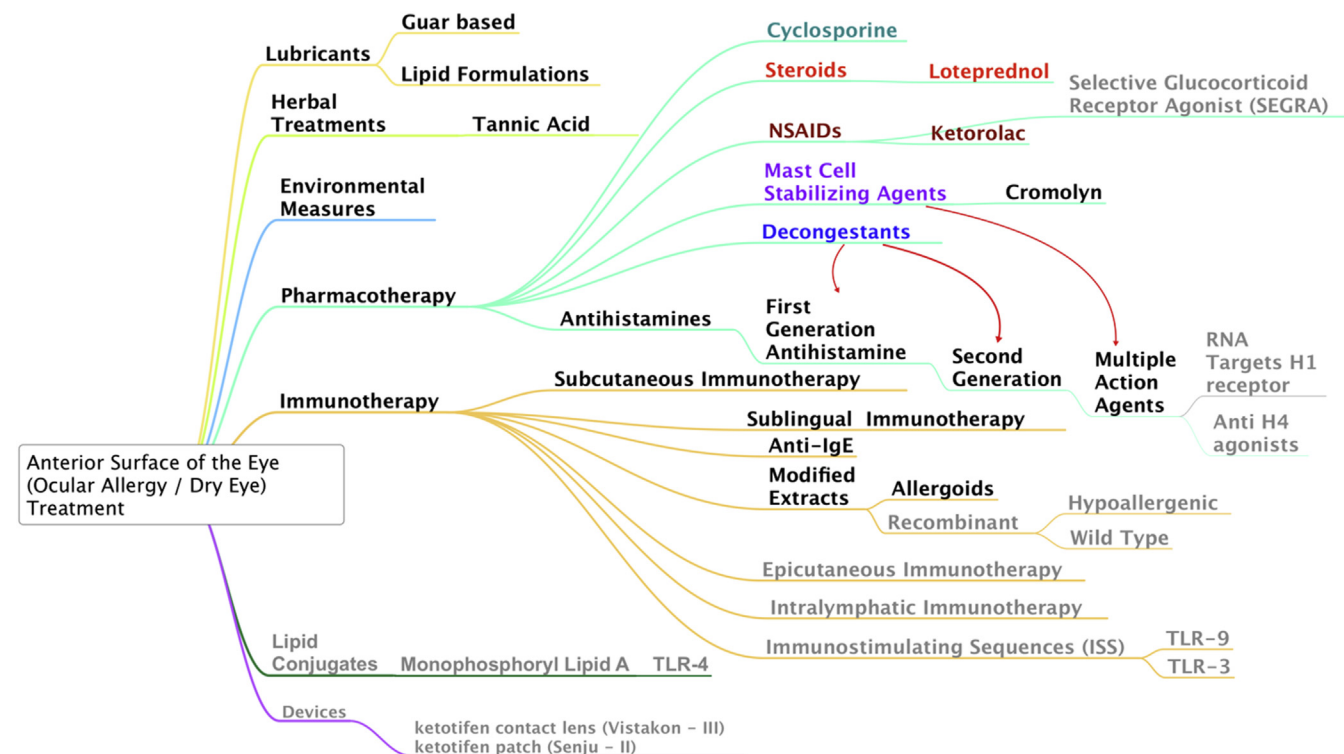


Figure 7. International Consensus summary of OA treatments. (A) Treatments for ocular allergy range from simple environmental measures to the use lubrication, pharmacotherapy, and immunotherapy. Pharmacotherapy involves medications with various actions (antihistamine with and without mast cell stabilizing effects [red arrow]) or the combination of medications (eg, decongestants with antihistamines [red arrows]) and the potential for future treatments using various devices (contacts lens containing medications), or other experimental treatments (noted in gray).

be made after eliciting a good history and does not require specialized equipment for diagnosis, fortunately, most misdiagnoses have no serious consequences for the patient, but they do lead to poorer QoL and decreased satisfaction with outcomes^{2,6,8,12} (Table 6).

Most OA patients self-treat with nonprescription medications for allergy symptoms. Even when diagnosed as allergic conjunctivitis by their primary care physician, the diagnosis is rarely confirmed by allergy testing. Patients seen by specialists (allergist/ immunologists, otolaryngologists, but not eye care specialists) are usually evaluated with allergy tests to implement environmental controls and with prescription medications (Fig 7). Subcutaneous and sublingual allergen immunotherapy improve long-term QoL in patients with OA.⁶ More treatment options have become available for the acute management of ocular allergic symptoms. These medications (eg, topical or oral antihistamines) have been designed to address either the onset symptoms or their duration of action.⁹⁹

In general, the management approach for acute and chronic forms of OA starts with allergen identification and avoidance, followed by nonpharmacological treatments, and finally progressing to pharmacological treatments (Table 7). These treatments include a variety of topical and oral agents, including antihistamines, mast cell stabilizers, corticosteroids, and other immunomodulators, including various forms of immunotherapy that can be offered under the guidance of specialists (Fig 8).

Ocular Surface Lubricating Agents

Irrigation of the ocular surface acts by diluting and removing allergens, minimizing the effect of allergen exposure on the ocular surface.^{10,90} In addition, some types of artificial tears provide relief through lubrication of the ocular surface via a combination of saline solution with a wetting and viscosity agent.¹⁸ If tear substitutes do not provide sufficient relief, ointments or time-released tear replacements, used at night, may provide a longer-lasting option, delivering ocular surface lubrication while the patient sleeps.¹⁰ These agents neither treat the underlying allergic response nor modify the activity of any of the mediators of inflammation.¹⁸ Thus, their use should be limited to mild seasonal/intermittent forms or exacerbations of more chronic persistent forms of ocular allergy.¹⁰⁰ A newer artificial tear formulation is composed of an aqueous lipid emulsion. The main benefit of the emulsion tears is the addition of oil onto the tear film, which helps prevent evaporation.

Oral Second-Generation Antihistamines

Overall, oral antihistamines can offer relief from the symptoms of OA but have a delayed onset of action. Newer, second-generation H₁ receptor (non or low sedating) antagonists are less likely to cause unwanted sedative or anticholinergic (dry eye) effects compared with earlier compounds.^{101–103} The concomitant use of an eye drop and a nonsedating oral antihistamine may be required

Table 7
Nonpharmacologic Therapy for Allergic Conjunctivitis

- Excessive rubbing should be avoided, because mechanical disruption of mast cells leads to degranulation and worsening of symptoms
- Application of cold compresses can help reduce symptoms, especially eyelid and periorbital edema.
- Lubrication with artificial tears several times throughout the day can provide lubrication and a diluting factor for the allergens on the ocular surface.
- Contact lens “holiday” during symptomatic pollen seasons because the allergenic proteins appear to adhere to the contact lens matrix
- Allergen avoidance using environmental control measures, which can include filtration systems such as air conditioning and closure of vents and windows during peak pollen seasons and for those with perennial allergen-induced conjunctivitis that include decreasing exposure to dust mite, cockroach, and animal dander

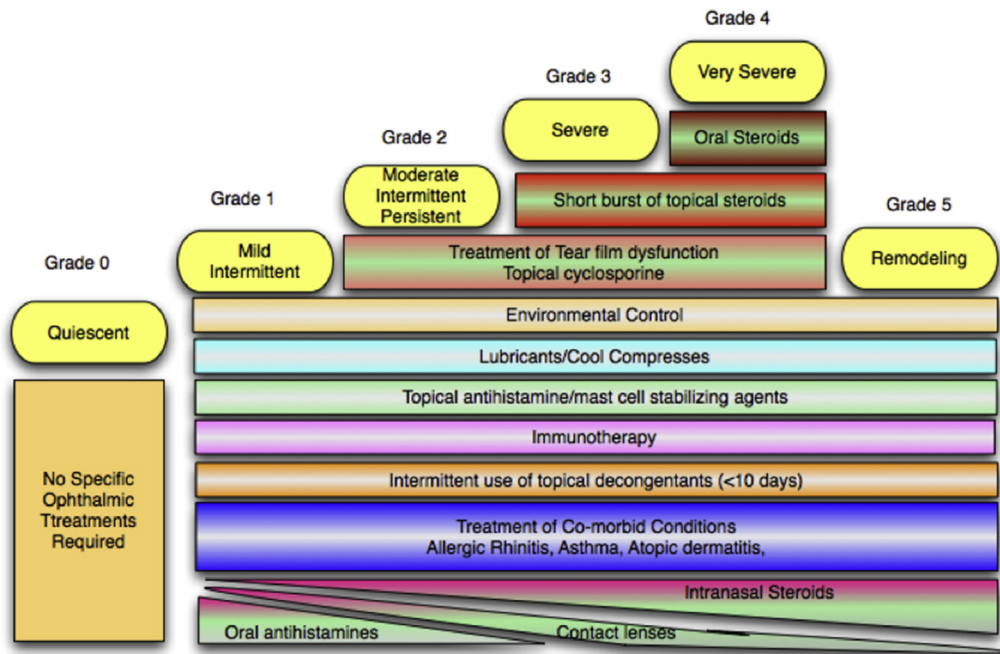


Figure 8. Stepwise approach to the treatment of various forms of allergic conjunctivitis. (A) The stepwise approach provides an overview of suggested treatment interventions that also includes and comorbid disorders.

to maximize the treatment of ocular allergic symptoms.⁹⁴ Second-generation antihistamines are preferred over first-generation antihistamines for the treatment of allergic conjunctivitis.^{104–108}

Most patients (>80%) with allergic rhinitis or allergic conjunctivitis have symptoms of both diseases. With nasal congestion being the number 1 complaint, followed closely by ocular symptoms, intranasal corticosteroids have demonstrated a positive effect on both symptoms.^{109–114} Several meta-analyses of randomized controlled trials found no significant difference in the degree of improvement of eye symptoms with the use of intranasal corticosteroids or oral antihistamines, including nonsedating antihistamines.^{111,115} The intranasal steroid (INS) used in recommended doses are generally considered safe and are not associated with long-term, clinically significant or irreversible side effects.^{116,117} However, in a retrospective chart review of 12 glaucoma patients using nasal corticosteroids, changes in intraocular pressure have been reported.¹¹⁸ Although the assessment of the quality of the evidence (AMSTAR2) from 5 systemic reviews evaluating INS for ocular symptoms associated with allergic rhinitis was recently reviewed,¹¹⁹ the effect of “long-term” chronic use of INS on the eye has not been well studied.¹¹⁷

Leukotriene Antagonists

Oral-leukotriene modifiers as a class of the nonsteroidal anti-inflammatory agents, alone, or in combination with antihistamines, have proved useful in the treatment of allergic rhinitis. Although they have been shown to decrease nitric oxide levels in the conjunctiva,¹²⁰ they have limited use for the treatment of OA.^{121,122}

Topical Decongestants

Topical decongestants reduce some signs and symptoms of allergic conjunctivitis through vasoconstriction via α -adrenergic stimulation.¹⁰ This action results in reduction of hyperemia, chemosis, and ocular redness through constriction of blood vessels supplying the eye.¹²³ Topical decongestants do not reduce the allergic response because they do not antagonize any of the

mediators of allergic inflammation. Prolonged use of topical decongestants as well as discontinuation of these agents after prolonged use can lead to rebound hyperemia (“conjunctivitis medicamentosa”).^{95,123} To minimize this potential side effect, topical decongestants should be used for as short a duration as possible (days vs weeks).¹²⁴ Oral decongestants have minimal effects on ocular injection and are contraindicated in pregnancy.¹²⁵

Topical Antihistamine/Decongestant Agents

Topical antihistamines and decongestants have different, but complementary and synergistic, mechanisms of action. Combinations of these 2 classes of medications have better efficacy than either agent alone.^{95,123} However, these combination agents generally have a shorter duration of action and still give rise to decongestant side effects, such as rebound hyperemia, with continued use. Therefore, use of these agents is recommended for a limited time to minimize the potential for side effects such as conjunctivitis medicamentosa.^{95,100,123} Dosing is 1 to 4 times daily from 3 years and older. However, topical decongestants may induce epiphora (excessive tearing), lacrimal puncta occlusion, dryness, and mydriasis (alpha agonists).

Mast Cell Stabilizers

Mast cell stabilizers prevent degranulation of mast cells, release of preformed inflammatory mediators, and synthesis of additional inflammatory mediators. They block both early and late phases of the ocular surface allergic response.¹²⁶ Mast cell stabilizers reduce hyperemia, itching, and irritation, although efficacy in ocular allergy varies among different agents.^{123,127} To provide this effect, mast cell stabilizers are most effective when administered before triggering of the allergic reaction, that is, prophylactically,^{126,127} although patients may notice some improvements in various forms of ocular allergy signs and symptoms within 24 to 48 hours if they are used after exposure to the allergen.⁹⁹ Mast cell stabilizers require a long loading period, during which they must be applied routinely for several weeks for optimal prophylactic benefit.¹²⁶ As a result of this required long regular dosing, patient compliance may

Table 8
Topical Multiple Action Agent Treatments for Ocular Allergy

	Azelastine HCl 0.05% (Optivar)	Epinastine HCl 0.05% (Elestat)	Ketotifen fumarate 0.25% (Zaditor)	Olopatadine HCl 0.1%(Patanol) 0.2%(PataDay) 0.7% (Pazeo)	Bepotastine besilate (Bepreve)
Indication	Relief of itching associated with allergic conjunctivitis	Relief of itching associated with allergic conjunctivitis	Temporary prevention of itching of the eye caused by allergies	Relief of itching associated with allergic conjunctivitis	Treatment of itching associated with allergic conjunctivitis
Dosage	1 drop each affected eye twice per day	1 drop each affected eye twice per day (age 3 and older)	1 drop each affected eye every 8-12 h	1 drop each affected eye once per day	1 drop each affected eye twice per day (age 2 and up)
Adverse event	Transient stinging (~30%), headache (~15%), bitter taste (~10%)	Cold symptoms (~10%), URI (~10%)	Headache (~10%-25%), Conjunctival injection (~10%-25%), Rhinitis (~10%-25%)	Cold syndrome (~10%), Pharyngitis (~10%)	Taste (~25%)

be a problem.¹²⁶ Topical mast cell stabilizers are generally safe and have minimal ocular side effects, although there may be some tolerability concerns, because transient burning or stinging may occur on application, and some may permanently stain clothing. Several studies have shown their effect in treatment of corneal involvement in VKC patients.¹²⁸⁻¹³²

Topical Antihistamines with Multiple-anti-inflammatory Activities

Some multiple-action agents provide relief through inhibition of mast cell degranulation as well as competitive binding of the H₁ receptor to block histamine binding and other cytokines.^{18,100,131,132} These agents have a rapid onset of antihistamine action, usually within 30 minutes after application, and therefore improve patient compliance compared with pure mast cell stabilizer agents.^{18,100} Several drugs with antihistamine and mast cell stabilizing activities generally provide relief of the itching associated with OA.¹³³ As a result of these attributes, combination products are currently the most commonly prescribed group of agents, because they are generally well tolerated and can be used for longer-term treatment of SAC.¹²³ Side effects are generally mild and include headache, cold-like symptoms, burning, stinging, and possible transient dysgeusia (bitter taste)^{100,133} (Table 8).

Nonsteroidal anti-inflammatory drugs (NSAIDs) block the cyclooxygenase enzyme and the production of prostaglandins from arachidonic acid. They reduce mucus secretion, cellular infiltration, erythema, and chemosis, as well as improve ocular itching.^{18,54,90,126,127,133} Ketorolac was the first to be approved for OA for improving the itch; however, as with other NSAIDs, it was associated with discomfort on instillation (ie, stinging and burning) that could decrease patient compliance.^{18,126,127} Unlike topical corticosteroids, NSAIDs (eg, ketorolac) do not mask ocular infections, affect wound healing, increase intraocular pressure (IOP), or contribute to cataract formation. They still should be closely monitored, because corneal melting and perforation have been described as occasional side effects.¹³⁴

Topical Corticosteroids

The most effective therapeutic responses in OA are with topical corticosteroids.¹³⁵ Corticosteroids relieve the signs and symptoms of all phases and forms of ocular allergy by nonspecific anti-inflammatory effects within 6 hours after application.^{136,137} Because corticosteroids provide effective relief of a broad range of signs and symptoms of ocular inflammation, these agents are considered an effective treatment option for all forms of ocular allergy.^{10,18,90,123,126,133,138} However, topical corticosteroids are not commonly used because of a fear of associated ocular side effects. These effects include increasing IOP and possible induction or exacerbation of glaucoma, formation of cataracts, delayed wound healing, and increased susceptibility to infection or superinfections.^{136,139} Development of increases in IOP and glaucomatous changes with use of corticosteroids may vary depending on whether the patient is a “steroid responder,” which is linked to a family history of glaucoma.^{139,140} Approximately 5% of the population will be “high responders,” with an increase in IOP greater than 15 mmHg after daily administration of corticosteroids for 4 to 6 weeks of treatment.¹⁴⁰⁻¹⁴² As a result, most guidelines recommend that their use be limited to more severe forms of OA or severe exacerbations of the more milder forms that are not controlled by other treatments and that these agents be used for as short a duration as possible.^{10,90,126,133,138} Only patients with more chronic forms of allergic conjunctivitis uncontrolled with other agents should use topical corticosteroids on a daily basis. Ophthalmologic consultation should be obtained for any patient using ocular corticosteroids for more than 2 weeks to assess cataract formation or increased IOP. Consultation is also merited for any persistent ocular

complaint or if the use of strong topical corticosteroids or systemic corticosteroids is being considered.³¹ The side effect profile of most corticosteroids limits their use. Although physicians use corticosteroids in all other areas, they are reluctant to use the old ketone corticosteroids in the eye because of side effects, especially IOP elevation. However, with the advent of a newer, safer and C-20 ester-based corticosteroid (eg, loteprednol etabonate), it is now possible to treat ocular allergic conditions with corticosteroids without the side effect of elevated IOP. The development of locally active agents such as SEGRAs (selective glucocorticoid receptor agonist) may lead to additional therapies with the efficacy of corticosteroids, but without the drawbacks.^{143,144}

Immunomodulating Agents: Topical Cyclosporin/Tacrolimus

Immunophilins are primarily used in the control of T-cell-mediated disorders. Topical cyclosporin and tacrolimus are approved in Japan for treatment of severe VKC and AKC. A recent multicenter study was conducted of the treatment of VKC with immunomodulating agents, but full results are still not available; preliminary data published in 2012 showed 0.1% tacrolimus and 2% cyclosporine drops to be efficacious in the treatment of VKC.¹⁴⁵ Topical cyclosporin 0.1% has been recently approved in the European Union and Canada as an orphan drug for the treatment of severe VKC.¹⁴⁶ Topical creams with tacrolimus or picrolimus are available for the treatment of the eyelid skin in atopic dermatitis, but the caveat is that the dermatological formulations commonly cause conjunctival surface irritation if they spill onto the conjunctiva.

Allergen Immunotherapy

Immunotherapy had been used for primary treatment of allergies, before the discovery of antihistamines and other pharmacological agents. In the original report, allergen immunotherapy “measured the patient’s resistance during experiments of pollen extracts to excite a conjunctival reaction.”^{147,148} The eye and not the skin was the target organ. The efficacy of subcutaneous allergen immunotherapy is well established, with most studies demonstrating reduction in nasal symptoms more than ocular symptoms.¹⁴⁹ Sublingual immunotherapy (SLIT) has also induced improvement in ocular symptoms, but the use of SLIT in many studies required significant eyedrop use.¹⁵⁰

The effect of immunotherapy specific for Japanese cedar (*Cryptomeria japonica*) pollinosis was to reduce daily total symptom medication score not only in cedar but also, at least modestly, in the cross-allergenic Japanese cypress (*Chamaecyparis obtusa*) pollination season.¹⁵¹ Thus, immunotherapy plays more of an important role in the “long-term” control of rhino-conjunctivitis. In allergic patients who had asthma and rhino-conjunctivitis when exposed to specific animal dander (Fel d I allergen), immunotherapy has been shown to improve overall symptoms of rhino-conjunctivitis and decrease anti-allergy medications. This same study was able to demonstrate a 1-log (10-fold increase) in the dose of allergen to induce a positive ocular conjunctival test reaction after 1 year of immunotherapy with the cat allergen.¹⁵² Clinical improvement and a reduction in allergen sensitivity was also noted in a 12-month immunotherapy study using a purified and standardized preparation of *Dermatophagoides farinae*. Patients receiving immunotherapy injections significantly improved in their subjective symptoms ($P < .028$) as well as in objective cutaneous ($P < .0001$) and conjunctival ($P < .001$) sensitivities.¹⁵³ In a ragweed immunotherapy study over the course of 2 years, nasal symptoms responded more than the ocular symptoms when compared with controls.¹⁵⁴ Although initial studies of allergen immunotherapy did not specifically address ocular symptoms,¹⁵⁵ more recent clinical studies in both subcutaneous and sublingual immunotherapy have

started to identify improvement in ocular signs and symptoms as a separate endpoint.^{156–162} In a recent study, the clinical effect on rhinitis and conjunctivitis achieved during specific subcutaneous immunotherapy persisted for years after termination of treatment (5-year follow-up). The visual analog scale reflected a 2- to 3-fold improvement for both ocular ($P < .001$) and nasal scores ($P < .01$), whereas the conjunctival sensitivity as measured by provocation tests was significantly reduced by more than 2 logs of allergen from years 2 through 5 ($P < .001$).¹⁶³ Similarly, in the studies using SLIT, there seems to be greater symptom reduction in allergic rhinitis than in allergic conjunctivitis. However, in a large meta-analysis, SLIT reduced the total and individual ocular symptom scores in subjects with allergic rhinitis and allergic conjunctivitis. Participants receiving active treatment demonstrated an increase in the threshold dose for the conjunctival allergen provocation test, but there was no significant reduction in ocular eye drops use.^{150,164} In another systematic review of subcutaneous immunotherapy on seasonal allergic rhinitis, the effect size on ocular symptoms was even higher than the effect size on nasal symptoms.¹⁶⁴

Contact Lenses

Patients who have seasonal allergy are commonly told to avoid contact lens use during seasonal flare-ups. However, contact lenses have certain benefits but require caution in patients with OA. One of the primary treatments of any inflammatory response is the use of a mechanical barrier, ie, a bandage. Bandaging the ocular surface is commonly used in the treatment of corneal abrasions to keep the “eyelid” as a bandage to promote faster healing of the damaged cornea. In a study evaluating the impact of daily disposable lenses vs patient’s standard chronic wear lenses, 67% reported that the daily disposable lenses provided improved comfort when compared with the chronic wear lenses they wore before the study. When patients were provided with a new pair of chronic wear lenses, 18% reported improved comfort, suggesting that the use of 1-day disposable lenses may be an effective strategy for managing OA in contact lens wearers.¹⁶⁵ The newer soft silicone with increased gas permeability contact lenses have a higher satisfaction of comfort (56%) than rigid gas-permeable lenses (14%), with 63% of nonatopic and 47% of atopic subjects describing their lenses as very comfortable to wear.^{166,167} The need for clean lenses with minimal deposit buildup must be stressed. Therefore, the recommendation for daily disposable lenses should be considered for all patients with OA.¹⁶⁸

Ocular Surface Treatment

For topical ocular treatments, the recommendation is for 1 drop at a time, with closure of the eyelids for a few seconds after drug instillation. When multiple eye drops are to be used, allow time between individual medications (3–5 minutes) to permit proper absorption of the medication into the ocular tissue and to prevent washout. The placement of more than 20 μ L at a time will lead to spillage and waste of medication. A drop is approximately 10 μ L. This increases absorption into ocular tissues, while excessive repetitive blinking causes topical medications to wash out of the ocular surface faster.

Complementary Treatments

Most herbal preparations contain several components that can potentially have a spectrum of physiologic and pharmacologic effects, both positive and negative. In Europe, several eye drop products contain chamomile extracts that cross-react with ragweed and thus may worsen symptoms in some patients. Many brand-name products contain a similar core of components with 1 or 2 minor differences and thus share similar clinical effects and

Table 9
Ocular Allergy Treatment Summary

- Identification and avoidance of irritants and sensitizing agents is the most effective way to prevent ocular allergy.
- Cold compresses (and refrigerated topical medications)
- Lubricants help to remove and dilute allergens that come in contact with the ocular surface.
- Oral second-generation antihistamines should be preferred over first-generation antihistamines for the treatment of allergic conjunctivitis.
- In cases of dry eye, first-generation oral antihistamines are to be discontinued.
- Among the newer, nonsedating antihistamines, no single agent has been conclusively found to achieve superior overall response rates.
- Topical antihistamines are effective in the treatment of allergic conjunctivitis.
- Topical decongestants should not be used long term because of a potential “paradoxical effect.”
- Topical cromolyn sodium has been the prototypic compound among mast cell stabilizer.
- Topical dual or multiple actions newer drugs are widely and effectively used in the treatment of ocular allergy.
- Topical NSAIDs, although effective in treating ocular allergy, may cause ocular and systemic side effects.
- The use of topical steroids should be restricted to brief courses for the most severe forms of ocular allergies.
- Increasing evidence has been accumulated indicating that intranasal corticosteroids reduce ocular symptoms associated with allergic rhinitis.
- Topical cyclosporin A and other immunomodulators have been used in the most severe chronic forms of ocular allergy (eg, allergic and vernal keratoconjunctivitis).
- Allergen immunotherapy should be considered for patients with allergic conjunctivitis and associated allergic rhinitis.
- Treatment of ocular allergy in pregnancy should consider the safety profile of drugs where data is available from the US Department of Food and Drug Administration or European Medicines Agency.
- Independently from the clinical phenotype of allergic conjunctivitis, the treatment of ocular allergy should follow a stepwise approach on the basis of actual clinical severity of signs and symptoms.

adverse effects. This makes it extremely difficult to ascribe a specific clinical or physiologic property to a specific herbal preparation. The World Health Organization has developed monographs on selected medicinal plants to provide scientific information on the safety, efficacy, and quality control of widely used medicinal plants. Lack of regulatory reform in the herbal industry makes it difficult for the clinician to provide informed advice about which agents to use.

Yuping feng granules in conjunction with cromolyn eye drops have been shown to further reduce ocular allergy symptoms effect. Yupingfeng granules is a concoction comprising several herbal roots from *Astragali* (Mongolian milkvetch), *Atractylodes* (sunflower), and *Saposhnikovia* (perennial Mongolian herb).¹⁶⁹

Quercetin, a bioflavonoid, is one of the components of an *Artemisia abrotanum* intranasal spray. In a small uncontrolled study, it was administered to 12 patients with allergic rhinitis, conjunctivitis, or asthma.¹⁷⁰ All subjects reported improvement in symptoms within 5 minutes of application, with continued improvement for several hours. Ocular symptoms also improved with intranasal application.

Perilla frutescens, an Asian herb, enriched with a preparation of rosmarinic acid, was studied in a randomized placebo-controlled trial of seasonal allergic rhino-conjunctivitis. Although a significant difference was seen in QoL with the higher dose of *P. frutescens* compared with placebo, the specific nasal and ocular symptoms were not statistically different (Table 9).^{171,172}

Summary Points

Oral and topical antihistamines continue to be the mainstay of therapy for OA, with ophthalmic corticosteroids being reserved for patients with severe symptoms under the care of allergists and eye specialists. The use of oral antihistamines should be closely monitored, especially in the elderly, because those have been found to have some degree of anticholinergic activity, and thus they may increase ocular dryness that also progresses with age. Subcutaneous immunotherapy is recommended in moderate to severe OA symptoms, because an improvement in exposure to 10- to 100-fold allergen concentrations in conjunctival provocation studies has been demonstrated. Further advances in immunotherapy, including DNA vaccines and alternative routes of administration, may lead to improved safety and allergen desensitization, with further improvement in OA symptoms.

Non-vision-threatening red or pink eyes include subconjunctival hemorrhage, OA, infectious conjunctivitis, blepharitis, dry eye, and corneal abrasion. Typical complaints offered by patients with such

entities include burning, itching, a scratchy sensation, eyelid tenderness, or ocular discharge. A history of burning is very nonspecific and is usually not a definitive sign of specific ocular disease. Itching tends to suggest an allergic cause, especially if accompanied by a thick ropy discharge. A scratchy sensation is frequently indicative of corneal/conjunctival foreign body, corneal abrasion, or dry eye. Purulent ocular discharge is usually associated with bacterial conjunctivitis. Patients with this disorder often complain of matted eyelids that stick together, especially in the early morning hours. Watery ocular discharge and a painful preauricular lymph node are characteristic of viral conjunctivitis. This disorder is extremely contagious and tends to follow an upper respiratory infection.

Causes of vision-threatening red or pink eyes are diverse and include acute angle-closure glaucoma, uveitis, herpes keratitis, corneal ulcers, and scleritis. These disorders are frequently associated with symptoms of ocular pain, blurry vision, and photophobia. In the presence of these symptoms, it is extremely important to rule out a history of trauma, recent eye surgery, or contact lens wear before the ocular examination.

Special Populations

There is a requirement for special considerations for ocular treatment for a number of special populations.

Elderly Patients

Conjunctivitis in the elderly may have the same causes common in other age groups, but also may be influenced by age-related physiologic changes, such as anatomic and mechanical changes. The use of oral antihistamines needs to be more closely monitored in the elderly, because it increases ocular dryness that also increases with age. Tear film dysfunction should be considered a major issue in this population.

Athletes

Athletic performance can be affected by allergic conjunctivitis, and appropriate management of symptoms with safe, effective, and permitted medications is needed to not compromise the athlete's performance ability or interfere with their ability to compete.

Pregnancy

Pregnancy is a unique situation, because one is commonly guided by the Food and Drug Administration and their older risk categories as well as newer information regarding medication use

and lactation. Limited data are available that any of the ophthalmic agents are found in breast milk. Oral decongestants should be avoided during the first trimester. Sodium cromolyn is a safe treatment for allergic rhino-conjunctivitis during pregnancy. Intranasal corticosteroids may be used in the treatment of nasal symptoms during pregnancy because of their safety and efficacy profile, and they have a potential positive impact on ocular allergy. It has been recommended that allergen immunotherapy not be started during pregnancy, but maintenance immunotherapy may be continued during pregnancy.

Allergic Conjunctivitis Unmet Needs

Major unmet needs in this area include under- or misdiagnosis and undertreatment.

The prevalence of allergic conjunctivitis is high, but application of adequate treatment is poor, because it remains a primarily self-diagnosed condition leading to self-treatment. There is a lack of understanding of the broad nature of allergic symptoms and the link between the allergic disorders, so a holistic approach is not taken with self-management. Primary care physicians limit their approach to allergic conjunctivitis management because of the lack of clear “best practice” guidelines. One major area of deficiency is the lack of head-to-head studies of various agents to provide the best choice of topical anti-inflammatory therapy for the individual patient. There is a need for improved and clear diagnostic criteria for primary care. More advanced guidelines are required for subspecialists to refine the differential diagnosis of anterior ocular surface disease (eg, allergy vs dry eye) and for appropriate cross-referral between specialists (allergists and eye care specialists) to maximize patient care and outcomes.¹⁷³ Allergists tend to underdiagnose dry eye disease while overdiagnosing ocular allergy. In general, ocular allergy is commonly overdiagnosed and undertreated by eye care professionals and underdiagnosed and undertreated or mistreated by primary care physicians, who frequently may treat these patients with ocular corticosteroids. Many of the referrals from eye care specialists to allergists represent skin test–negative ocular surface disorders that actually reflect the presence of a form of dry eye syndrome or other ocular surface inflammatory disorders, because many of these patients have excessive tearing and irritation of the ocular surface mimicking ocular allergy.

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