



Allergic conjunctivitis: an update on diagnosis and management

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Purpose of review

The focus of this review is to provide a logical paradigm for the diagnosis and treatment of ocular allergies, with a focus on seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC).

Recent findings

Several classes of topical medications are currently available for the management of ocular allergies, including: lubricating agents, vasoconstrictors, antihistamines, mast cell stabilizers, and topical corticosteroids.

Summary

SAC and PAC make up the vast majority of ocular allergy cases. A proactive approach to these diseases, anticipating the regional spring and fall allergen spikes, is needed for optimally managing these disorders. A multifaceted treatment regimen comprising patient education, lifestyle modification, and topical medications (such as antihistamines and/or mast cell stabilizers and corticosteroids) may be required in order to manage ocular allergies effectively. The appropriate treatment paradigm is based on the severity of the patients' signs and symptoms. For moderate-to-severe cases, especially chronic vernal keratoconjunctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis, comanagement with an ophthalmologist is recommended.

Keywords

allergic conjunctivitis, ocular allergy, perennial allergic conjunctivitis, seasonal allergic conjunctivitis

INTRODUCTION

Allergic conjunctivitis is a group of ocular surface diseases that are typically associated with type 1 hypersensitivity reactions [1]. Allergic conjunctivitis is often underdiagnosed [2], as it is a comorbid condition of rhinitis and asthma [3]. It can also be difficult to differentiate allergic conjunctivitis from other ocular surface disorders, as these may share some of the same signs and symptoms. Studies have estimated the prevalence of allergic conjunctivitis to range between 15 and 40% of the population [2]. The onset of seasonal allergic conjunctivitis (SAC, also called hay fever conjunctivitis [4]), the most common form of allergic conjunctivitis, coincides with regional seasonal increases in circulating allergens, such as grass pollens [5]. SAC is not generally considered to be serious or sight-threatening but causes much discomfort and loss of productivity during the spring and fall allergy seasons. Individuals with perennial allergic conjunctivitis (PAC) experience symptoms throughout the year; however, seasonal spikes can occur [5]. SAC and PAC comprise most of the allergic conjunctivitis cases

(about 95% in the United States) [6] and will be the focus of this review.

Both SAC and PAC are IgE-mediated events for which the mast cell response leads to the release of histamine, leukotrienes, prostaglandins, and other mediators [7]. The acute response is rapid, usually taking place within 30 min. An upregulation of adhesion molecules follows, with an increased infiltration of inflammatory cells (i.e. mast cells and eosinophils) into the conjunctival epithelium [1]. During the delayed phase, additional mast cell activation occurs within the conjunctiva, which increases the severity of the response.

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KEY POINTS

- SAC and PAC are the most prevalent types of allergic conjunctivitis (about 95% of cases in the United States).
- The hallmark signs and symptoms of both SAC and PAC are itching (pruritus) and redness, respectively.
- A more proactive treatment approach for allergic conjunctivitis is recommended (i.e. anticipating the spring and fall allergy seasons) to protect patients and minimize the sequelae of the disease.
- A multifaceted treatment regimen consisting of patient education, lifestyle modification, and topical medications (such as antihistamines and/or mast cell stabilizers, corticosteroids, and immunomodulators) should be used to manage ocular allergies.

The other types of allergic conjunctivitis (other than SAC and PAC) are considered more serious, and referral to an ophthalmologist is generally warranted. Chronic vernal keratoconjunctivitis (VKC) is associated with conjunctival scarring, eyelid thickening, ptosis, corneal neovascularization, ulceration, thinning, infection, keratoconus, and vision loss [8]. Individuals suffering from atopic keratoconjunctivitis (AKC) can experience eyelid tightening, loss of eyelashes, and cataracts in addition to the sequelae mentioned for VKC. Giant papillary conjunctivitis (GPC) is associated with eyelid inflammation, which can cause ptosis or a drooping of the eyelid.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of allergic conjunctivitis can be challenging because of the wide array of disorders that can mimic or mask the condition, including: bacterial conjunctivitis, rhinitis, dry eye, meibomian gland disease (resulting in tear film abnormality or insufficiency), and blepharitis. A medical history and assessment of environmental risk factors are the first steps to achieving an accurate diagnosis. The following specific items [8] may provide valuable clues to reach an accurate diagnosis:

- (1) Signs and symptoms (itching, redness, and chemosis)
- (2) Symptom duration
- (3) Discharge
- (4) Unilateral or bilateral presentation
- (5) Contact lens wear
- (6) Allergy, asthma, or eczema
- (7) Topical and systemic medication use (i.e. over-the-counter eyedrops and systemic allergy medications)

- (8) Compromised immune status
- (9) Systemic disease (current or prior)
- (10) Social factors (i.e. smoking, travel, and occupational)

In most cases, a diagnosis can be made based on the patient history and examination. Ophthalmic examination should focus primarily on the conjunctiva, a thin mucous membrane that extends from the eyelid margin to the border of the cornea and sclera. The conjunctival membrane is an active immunologic tissue that responds to allergic stimuli [9,10].

Environmental allergens trigger both SAC and PAC (Table 1) [5,8]. The hallmark sign and symptom of both SAC and PAC are itching (pruritus) and redness, respectively [11]. Others include burning, stinging, photophobia, tearing (epiphora), watery or mucoid discharge, chemosis, or dry eye [10,12]. When the signs and symptoms are consistent with SAC and patient history does not indicate some other disease, allergy testing is usually not required [4]. Cobblestoning [13,14] or papillary hypertrophy of the upper tarsal conjunctiva is a sign generally not observed in the SAC or PAC patient and indicates a more chronic and severe form of allergic conjunctivitis.

A proposed clinical severity grading classification of mild (0–1), moderate (2–3), and severe (4) has been created to facilitate and direct treatment of allergic conjunctivitis (Table 2) [15]. These severity grades range from mild (no overt signs)-to-severe (symptoms so pronounced that these interfere with daily functions). This model of classification can serve as a guide for designing the optimal treatment regimen for the allergic conjunctivitis patient.

TREATMENT

The primary methods used to evaluate ocular allergy medications are the conjunctival allergen challenge (CAC) and environmental studies [16]. The CAC model was developed as a modification of the conjunctival provocation test [17] to minimize variability seen with the allergen challenge model [16]. The CAC model appears to provide comparable results to environmental studies [18] within a more controlled setting especially when evaluating topical antihistamines.

Numerous classes of agents, both systemic and topical, have been used to manage the signs and symptoms of allergic conjunctivitis (Table 3) [19–20,21]. Ocular surface lubricants such as isotonic saline, artificial tears, and ointments help to rinse antigens from the eye. Many of these products

Table 1. Differential diagnosis for evaluating patients with allergic conjunctivitis

	Allergic conjunctivitis (seasonal and perennial)	VKC	AKC	Giant papillary keratoconjunctivitis
Predisposing factors	Environmental allergens	Hot, dry environments, and environmental allergens	Genetic predisposition and environmental allergens	Contact lens wear, irritation from exposed sutures, and prostheses
Signs				
Chemosis	+	±	±	±
Cobblestoning	–	++	++	++
Discharge	Clear mucoid	Stringy mucoid	Stringy mucoid	Clear white
Lymph node	–	–	–	–
Lid involvement	–	+	+	–
Predominant cell type	Mast cell eosinophil	Lymphocyte eosinophil	Lymphocyte eosinophil	Lymphocyte eosinophil
Symptoms				
Gritty sensation	±	±	±	+
Pruritus	+	++	++	++
Seasonal variation	+	+	±	±

Adapted from [5] and [8]. – absent; ± present or absent; + present; ++ pronounced. AKC, atopic keratoconjunctivitis; VKC, vernal keratoconjunctivitis. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

are available over-the-counter. However, these agents do not have direct efficacy on allergic mediators. These provide only temporary relief and have little or no effect on moderate-to-severe ocular allergy. They may also contain preservatives such that when used excessively, they can add insult to the already irritated ocular surface. Topical decongestants (vasoconstrictors) are α -agonists that act to reduce redness and edema. Overuse of these agents, however, can cause mydriasis (pupil dilation) and lead to rebound hyperemia of the

conjunctiva. Generally speaking, vasoconstrictors are not recommended for treating ocular allergies, as the topical antihistamines are safer and more effective [7[¶]].

In recent years, topical antihistamines have become the mainstay of management for allergic conjunctivitis. The benefits of these agents are that they block histamine, stabilize the mast cell, and inhibit eosinophil activation and migration [7[¶]]. Topical antihistamines address the signs and symptoms of ocular allergy, particularly itching. In a few

Table 2. Proposed classification of allergic conjunctivitis severity

Severity	Grade	Patient profile
Mild	0	Mild symptoms (i.e. grittiness, pruritus, and seasonal variation) No signs
Mild	1	Mild-to-moderate symptoms Few signs (i.e. redness, chemosis, and discharge)
Moderate	2	Moderate-to-severe symptoms Mild signs
Moderate	3	Severe symptoms Moderate signs Visual signs
Severe	4	Severe symptoms (interfering with visual function) Severe signs Visual signs

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Table 3. Topical medications for the treatment of seasonal allergic conjunctivitis

Generic name	Trade name	Class
Alcaftadine	Lastacaft	H1-antagonist/mast-cell inhibitor
Azelastine HCl	Optivar, generic	H1-antagonist/mast-cell inhibitor
Bepotastine besilate	Bepreve	H1-antagonist/mast-cell inhibitor
Cromolyn sodium	Crolom, generic	Mast-cell inhibitor
Emedastine difumarate	Emadine	H1-antagonist
Epinastine HCl	Elestat	H1- and H2-antagonist/mast-cell inhibitor
Ketorolac tromethamine	Acular, Acular LS, Acular PF	Nonsteroidal anti-inflammatory drug
Ketotifen fumarate	Alaway, Zaditor, Claritin Eye, Eye Itch Relief	H1-antagonist/mast-cell inhibitor
Levocabastine HCl	Livostin	H1-antagonist
Lodoxamide tromethamine	Alomide	Mast-cell inhibitor
Loteprednol etabonate	Alrex, Lotemax	Corticosteroid
Naphazoline	AK-Con, Albalon, Allerest, All-Clear, Antazoline-V, Naphcon, Clear Eyes, Comfort Eye Drops, Degest, Estivin II, Ocu-Zoline, Vasocon, VasoClear	Decongestant (vasoconstrictor)
Naphazoline/antazoline	Vasocon-A	Antihistamine/decongestant
Naphazoline/pheniramine	Naphcon-A	Antihistamine/decongestant
	Opcon-A	
	Visine-A	
Nedocromil sodium	Alocril	H1-Antagonist/mast-cell inhibitor
Olopatadine HCl 0.1%	Patanol	H-1 Antagonist/mast-cell inhibitor
Olopatadine HCl 0.2%	Pataday	H-1 Antagonist/mast-cell inhibitor
Pemirolast potassium	Alamast	Mast-cell inhibitor
Tetrahydrozoline	Visine	Decongestant (vasoconstrictor)

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cases these can cause local irritation and other side-effects, but these are more prevalent in older generation medications. Systemic antihistamines can be used, in some cases, but these medications tend to dry the ocular surface. For patients without comorbidities such as rhinitis, topical ophthalmic agents are preferred to administration of systemic antihistamines.

Mast cell stabilizers (inhibitors) prevent degradation of mast cells. These agents are particularly effective in SAC and PAC in which the predominant cell types are the mast cell and eosinophil. Mast cell stabilizers address both the early and late phases of the allergic response [6].

Combination antihistamine/vasoconstrictor (histamine blocker and α agonist) eyedrops are now available. These medications address itching, redness, and edema. Some tend to be slower in their onset of action, and relatively short acting. These can also cause sedation or excitability. Rebound hyperemia of the conjunctiva is also a concern.

A popular treatment in use today is the topical antihistamine/mast cell stabilizer (i.e. alcaftadine [22,23], azelastine [24–26], bepotastine

[27,28^{*},29–31], epinastine [32,33], and olopatadine [34–36]). These dual-acting medications relieve redness, hyperemia, itching, and irritation. They have a quick onset of action, which is likely to improve patient adherence compared with the pure mast cell stabilizers [37]. Several of these agents require only once-a-day or twice-a-day dosing. Side-effects, which tend to be transient and mild, include: stinging, burning, bitter taste, cold symptoms, and sedation.

NSAIDs can address the itching associated with allergic conjunctivitis; however, only ketorolac tromethamine 0.5% has a Food And Drug Administration (FDA)-approved indication for the treatment of SAC [7^{*}]. In general, NSAIDs are used in the management of postoperative pain and inflammation after cataract surgery but not as a first-line therapy for ocular allergies. These agents can cause discomfort upon instillation, which can in turn lead to reduced patient adherence [38].

Topical corticosteroids (i.e. loteprednol etabonate) inhibit the inflammatory process [8] and are used for the acute phase of the allergic response. These agents provide relief from most ocular signs

and symptoms of SAC. Historically, chronic corticosteroid use has been reported to carry a liability of increased intraocular pressure (IOP). However, loteprednol reportedly has a low propensity to cause elevations in IOP [39]. The risk of cataract formation historically associated with steroids is also low for the more recently developed molecules. In the case of loteprednol, the C-20 ester corticosteroid structure prevents the formation of Schiff base intermediates with lens proteins as occurs with C20 ketone corticosteroid molecules [19²²].

Optimally, the treatment of allergic conjunctivitis should be based on severity (Table 4). For the patient with mild signs and symptoms, education can be helpful in managing the disease. Many of the lifestyle modification factors that benefit ocular allergy sufferers are applicable to allergy sufferers in general, including [7²,11]:

- (1) Allergen avoidance – avoid being outdoors during times when pollen counts are high
- (2) Avoidance of animal exposure for sensitive individuals
- (3) Hypoallergenic bedding
- (4) Washing sheets in hot water, which denatures allergenic proteins (i.e. those from dust mites)
- (5) Showering and shampooing at bedtime to remove allergens
- (6) Sunglasses, which serve as a barrier to airborne allergens
- (7) Avoidance of eye rubbing – rubbing can introduce allergens into the eye and/or cause the release of more inflammatory mediators
- (8) Eyelid cleansers – foam cleansers and wipes help to remove allergens from the lids and lashes
- (9) Cool compresses – help to alleviate ocular itching

Table 4. Suggested treatment paradigms for allergic conjunctivitis

Severity	Treatment
Mild	Lifestyle modifications (i.e. allergen avoidance, eyelid cleansers, and cool compresses)
	Artificial tears
	H1 antagonist and/or mast cell stabilizer
Moderate	H1 antagonist/mast cell stabilizer
	Short course (2–3 weeks) corticosteroid
Severe*	Short course (2–3 weeks) stronger corticosteroids
	Topical antihistamines/mast cell stabilizers
	Immunomodulators

*Consider comanagement of these patients.

When optimizing lifestyle factors proves inadequate, artificial tears can help rinse allergens from the ocular surface. Finally, topical antihistamines and/or mast cell stabilizers can be prescribed to provide symptom relief.

In addition to the above treatments, other prescription medications can be added or substituted for patients with moderate allergic conjunctivitis. Topical antihistamines/mast cell stabilizer agents provide dual actions to eliminate the signs and symptoms of ocular allergies. Corticosteroids can be added to the regimen administered in a brief pulse fashion during the acute phase. Avoid certain ophthalmic preservatives (i.e. benzalkonium chloride) for patients who appear to be sensitive, particularly those suffering from chronic dry eye, as their ocular surface may already be compromised.

For patients with severe signs and symptoms, topical antihistamines/mast cell stabilizers in combination with a stronger corticosteroid may be warranted. Individuals in this group are candidates for referral/comanagement as their condition will require a more aggressive treatment approach. Immunomodulators, such as cyclosporine A, tacrolimus, and pimecrolimus inhibit calcineurin and can be used as replacement therapy for corticosteroids, when long-term therapy is required [4]. Tacrolimus ointment has been reported to reduce inflammatory cells, particularly eosinophils, in conjunctival cytology samples taken from atopic blepharoconjunctivitis patients [40]. Cyclosporine A has shown some benefit in patients with AKC and VKC [5,41]. However, it should be noted that these are off-label, unapproved uses of the product. The most common adverse effect of topical cyclosporine A is burning [42].

Treatment strategies for PAC are similar to those for SAC. Corticosteroids are beneficial for the early phase of treatment as pulse therapy [4,43]. Topical antihistamines/mast cell stabilizers are effective for maintenance therapy throughout the year. Patients taking topical or systemic antihistamines, who are prone to dry eye, should be monitored for worsening of their symptoms.

Allergen-specific immunotherapy (SIT) can be effective for patients with severe allergic conjunctivitis/rhinoconjunctivitis. Increasing doses of the allergen are administered by the subcutaneous immunotherapy (SCIT) or sublingual immunotherapy route to achieve hyposensitization [4]. Side-effects, including anaphylaxis, are known to occur with this form of therapy. SIT requires a long-term commitment from the patient and/or caregiver in terms of time (i.e. SCIT requires monthly injections for 3 years) and expense. This may not be practical

for the SAC patient who does not suffer from other comorbidities.

DISCUSSION

A proactive treatment approach for allergic conjunctivitis is warranted. This should ensure that SAC, for example, does not develop into chronic inflammation [4]. The clinician should make certain the ocular allergy patient has been thoroughly educated and provided with current prescriptions of the appropriate medications, such as dual-acting topical antihistamines/mast cell stabilizers, leading into the spring and fall allergy seasons. Climate change is expected to cause an increase in the pollen count over the coming years. SAC may become increasingly persistent and chronic, necessitating treatment for prolonged periods. For patients with moderate or severe symptoms and signs (grade 2–4), brief pulses of topical corticosteroid (i.e. loteprednol etabonate 0.2%) in combination with other dual-acting agents may provide superior and faster control of the ocular allergic response.

It is important to raise patient awareness of the sequelae of ocular allergies as some may question the need for treatment. Without treatment, individuals with ocular allergies may have to limit their daily activities such as reading, computer work, and being outside [12]. Prompt treatment can minimize the sequelae of allergic eye diseases and the associated loss of productivity (time away from school or work because of temporary visual impairment) [8].

The issue of patient adherence to allergy treatment regimen needs to be addressed. Numerous patient-related and treatment-related factors can cause a decrease in adherence [44,45]. The complexity of the treatment regimen, duration of therapy, efficacy, side-effects, and previous treatment failures can all affect the level of adherence. Patients must have adequate knowledge and the proper motivation in order to follow their treatment instructions.

Controlling and managing allergic eye disease often require a multifaceted approach, including patient education, lifestyle changes, and the appropriate medication regimen that is tailored to the severity of the disease. Comanagement in some allergic conjunctivitis cases may be recommended and is particularly important for patients with more severe forms of the disease. Referral to an ophthalmologist is generally recommended [11]:

- (1) When there is uncertainty in the red eye diagnosis
- (2) When the signs and symptoms persist or worsen

- (3) For those patients with more severe disease
- (4) Particularly when aggressive or long-term use of topical steroids is necessary as IOP should be monitored
- (5) When AKC, VKC, or GPC are suspected (these conditions can be vision-threatening and these often require chronic topical corticosteroid and other immunomodulatory treatment)

The majority of patients with allergic conjunctivitis clearly rely on self-diagnosis and self-medication [46]. Therefore, the clinician must arm the patient with adequate information and the proper medications to control the disease. Otherwise, the patient might simply revert to reaching for the least expensive and often least effective treatment. The patient may be inclined to use systemic antiallergic medications, which are often less effective than targeted ocular therapy. These agents can also dry the ocular surface and exacerbate any ongoing ocular surface disease.

CONCLUSION

In order to obtain the best outcomes and provide optimal relief for the patient suffering with allergic conjunctivitis, the clinician should rely on a proactive, targeted multifaceted approach based on severity of the disease. Anticipate the spring and fall allergy seasonal spikes in pollen counts and be prepared to treat the signs and symptoms that accompany them. This proactive approach should inhibit the inflammatory response before it becomes too severe and minimize the sequelae of allergic conjunctivitis. Comanagement with an ophthalmologist can be helpful for the more challenging cases, especially when vision is at risk. Patients with ocular allergy considering elective laser vision correction or cataract surgery should be well controlled in advance of the planned procedure [15]. The overall goals for the treatment regimen in the allergic conjunctivitis patient are improved patient care and quality of vision, through better control of the allergic condition, with fewer signs and symptoms, fewer days away from school and work, resulting in a better overall quality of life.

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Conflicts of interest

Prof O.'B. serves as a non-salaried ad hoc consultant to Bausch and Lomb.

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