

Diagnosis and Management of Allergic Conjunctivitis

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Abstract

Purpose of the review The purpose of this review is to define the classification, diagnosis, and management in adults and children with allergic conjunctivitis with emphasis on recent findings.

Recent findings Current literature divides allergic conjunctivitis according to severity and frequency, facilitating its diagnosis, study, and treatment choices. Novel pharmacological therapies aim at inhibiting inflammatory pathways at a specific molecular level and include selective glucocorticoid receptor agonists, kinase inhibitors, and IL-1 receptor antagonists.

Summary Ocular allergies are a group of heterogeneous diseases with varied immunological mechanisms and clinical presentation. Allergic conjunctivitis is an immune-mediated type I hypersensitivity disorder of the eye's surface. Clinical presentation is characterized by bilateral ocular itching, conjunctival erythema, and ocular edema. Diagnosis is fundamentally clinical and should be supported by evidence of an IgE-mediated mechanism using skin prick tests and/or serum antigen-specific IgE. Treatment encompasses non-pharmacological and pharmacological approaches. The preferred pharmacological medications are topical dual-acting agents, which have both local antihistamine and mast cell stabilizing properties.

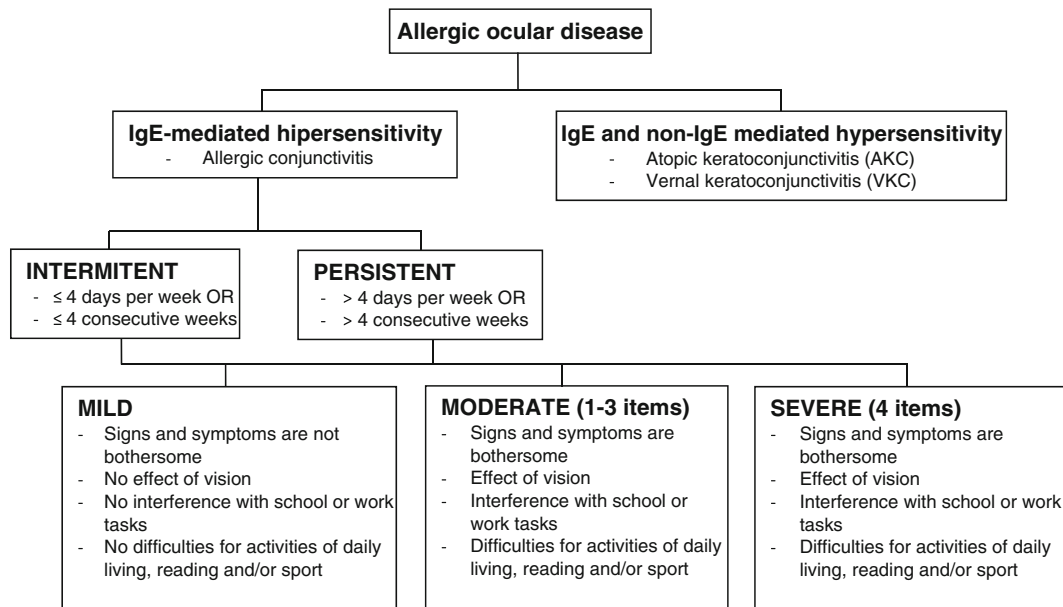


Fig. 1. Classification of allergic ocular disease

Introduction

Allergic conjunctivitis (AC) is a common ocular immune-mediated disorder. Its prevalence is difficult to establish from epidemiological studies, as many target rhinoconjunctivitis and not ocular symptoms alone [1]. It has been estimated to affect 10% of the worldwide population and has had a rising prevalence in Europe, due to the introduction of ragweed [1, 2•].

In Alergológica 2015, a Spanish prevalence study, rhinoconjunctivitis was considered the first reason for visiting an allergy specialist [3]. In ISAAC Phase III Study, 30% of children with allergic comorbidities (asthma, rhinitis, or eczema) also associated conjunctivitis [4•].

There is no unanimous definition or classification for ocular allergies, as they include a heterogeneous group of diseases with varied immunological

mechanisms and clinical presentations [1]. For this reason, aiming at improving evaluation, management, and control of ocular allergies, the Rhinoconjunctivitis Committee of the Spanish Society of Allergology and Clinical Immunology and the Spanish Ocular Surface and Cornea Group have recently published a consensus document on AC. In it, based on immune mechanisms, AC is considered an IgE-mediated disease; however, vernal keratoconjunctivitis and atopic keratoconjunctivitis encompass both IgE and non-IgE mechanisms [5••]. AC can be also classified into intermittent or persistent, according to the frequency and severity of symptoms, similar to the classification criteria for allergic rhinitis proposed in the “Allergic Rhinitis and its Impact on Asthma (ARIA)” document [5••, 6] (see Fig. 1).

Pathophysiology

AC is an inflammatory disease fundamentally caused by an IgE-mediated immune mechanism or type I hypersensitivity reaction. The conjunctival epithelial layer protects the eye from the external environment. When an allergen

permeates the conjunctival surface in sensitized patients, classic mast cell activation is triggered [2•, 7••]. Pollens are considered seasonal allergens, whereas house dust mites, animal dander, and environmental molds are considered perennial allergens [5••].

In the sensitization phase, an allergen is initially captured by an antigen-presenting cell (APC) and later presented with the class II histocompatibility molecules to the CD4+ T helper lymphocytes. Dendritic cells have been actively implicated as APCs in ocular allergy and other allergic diseases [7••]. The presentation prompts a Th2 lymphocyte population to expand and secrete a series of cytokines, which promote IgE synthesis from the B lymphocytes and other molecules. As a result, growth and differentiation of B cells is reinforced. The newly antigen-specific IgE in turn binds to the membrane of the conjunctival mast cells via high-affinity receptors [2•, 7••].

When a sensitized patient comes into contact with allergens, cross-linking of two IgE molecules occurs on the surface of mast cells. The cross-linking prompts mast cells to degranulate and release inflammatory mediators. It has been shown that continued allergen load leads to an increased population of resident mast cells in the conjunctival tissue of allergic patients, particularly during pollen season [2•]. Overall, several inflammatory mechanisms, including adhesion molecules, neurogenic factors, and cellular components, come together to orchestrate the allergic reaction [2•, 7••, 8].

In an early phase, mast cells release preformed mediators from their granules like histamine, proteoglycans, and neutral proteases. Furthermore, they synthesize new ones, such as prostaglandins, leukotrienes, platelet-activating factor, and tumor necrosis factor α [7••]. This early-phase reaction is mainly driven by histamine, which peaks its concentration in tears 5 min post-exposure. The reaction naturally remits over the course of 30–40 min [2•, 9].

A late-phase reaction develops approximately 6–72 h after allergen exposure and is a result of the accumulation of inflammatory cells within the conjunctiva. These include basophils, eosinophils, T cells, and neutrophils. Further IgE production, elevation of proinflammatory molecules, such as interleukin 4, and other T cell mediators preserve the reaction [2•]. New insights into the role of neurogenic mechanisms in the eye have shown that the immune system operates in close association with the nervous system. Neuropeptides act as mediators between both systems and contribute to maintaining an intraocular immunologically depressed microenvironment [7••].

Clinical presentation

Patients can present with clinical signs and symptoms of AC at any age and regardless of sex. Another clinically relevant fact is that AC frequently presents with other allergic comorbidities, mainly rhinitis and/or asthma. Nasal symptoms may be present in as much as 97% of children and 66% of adults. Similarly, asthma symptoms are seen in approximately 56% of children and 16% of adult populations [5••]. Seasonal symptoms are more often found in young adults between 20 and 40 years of age, without gender predilection [7••].

When the main symptom of AC, bilateral ocular itching, is absent, the need for a differential diagnosis must be considered by the clinician [10]. Other symptoms include lacrimation, burning, and foreign body sensation. In severe

cases, blurred vision and photophobia can be encountered. It has been proposed that blurred vision can be due to alteration of the composition and stability of the tear film [7••, 10]. Pain and visual disturbances suggest corneal involvement and VKC and AKC must be ruled out by an ophthalmologist [11••].

The physical examination can reveal conjunctival hyperemia, edema of the conjunctival surface, a pale pink palpebral conjunctiva with or without hypertrophic papillae, and watery or serous discharge [7••, 11••]. Clinical signs can be assessed using a slit lamp or a light source combined with fluorescein staining, to aid in the detection of ocular surface disruption [5••].

Diagnosis

The diagnosis of AC is essentially clinical, based on a concordant case history and physical examination. In atypical or severe cases, examination by an ophthalmologist is required. Further studies to demonstrate an IgE-mediated mechanism and confirm a culprit allergen should be carried out, when possible, in all patients to confirm the diagnosis [10, 11••].

Confirmation can be sought through positive results in skin prick tests (SPTs) with suspected pneumoallergens or elevation of serum-specific IgE to whole allergens or their purified molecular components. SPTs should be carried out according to EAACI recommendations. Up to 24% of patients can be sensitized to multiple allergens, thus clinical relevance must be established by the clinician [5••, 11••].

In some cases, the skin prick tests and serum IgE may be negative, and a conjunctival allergen provocation test with suspected allergens may be performed. A provocation test may be useful as well to determine allergen relevance in polysensitized patients. Furthermore, levels of free specific IgE, total IgE, cytokines, and other inflammatory markers can be measured in tear fluid; however, these are not useful in routine clinical practice and are best suited for research purposes [5••, 11••].

The “Consensus Document on Allergic Conjunctivitis” indicates that another criterion to support the diagnosis of AC is to evaluate the response of the patient to topical antihistamines or mastocyte stabilizers [12]. This therapeutic challenge may be useful in both adults and children, particularly those with negative test results and suggestive clinical history.

Table 1 exemplifies the different diagnostic tools currently available for the evaluation of patients with probable allergic conjunctivitis.

Treatment

The treatment of AC comprises both non-pharmacological and pharmacological measures. Non-pharmacological measures comprise specific actions to reduce exposure to environmental allergens. These can include barrier methods such as wearing glasses when going outside in the pollen season or the use of dust mite covers for the beddings. Other non-pharmacological measures include the application of cold compresses and artificial tears on the eyes to provide relief [13].

Table 1. Diagnostic tools in allergic conjunctivitis

	Aim	Instruments	Recommendations
Clinical history	Evaluate patient's symptoms, frequency, and severity Patient's personal and family history of atopic disease Environmental factors: exposure to allergens or irritants	Patient interview	Accurate medical history Guided medical history Refer to ophthalmologist in unusual or severe cases; signs of visual disturbance; ocular pain
Ocular examination		Assess ocular signs and look for possible allergic comorbidities	Observation with natural light or light source Eversion of eyelid technique Use of slit light Use of fluorescein staining
Examination of the eye, eyelid and periocular skin	ophthalmologist may be required in severe or atypical cases		
Examination by Allergy tests	Evaluation of allergy sensitivity and determination of possible culprit allergen or allergens provocation test	Skin prick tests Blood analysis for determination of serum total IgE, allergen-specific IgE, molecular allergen diagnosis Evaluate the conjunctival response to specific allergens	If possible, perform on all cases with suspicion of allergic conjunctivitis Provocation by topical allergen at fixed dilutions
Conjunctival allergen			
Evaluate use in SPT and	IgE-negative cases Evaluate use in polysensitized patients to assess allergen relevance For evaluation of desensitization therapy		
Ocular/tear sampling	Obtain tear fluid, cells, or tissue for analysis	Tear collection Scraping Brush Cytology Biopsy	Used in experimental and clinical studies Not recommended for routine cases

Pharmacological measures can be divided into topical and systemic treatments, according to the route of administration of the medication.

Topical treatments for AC

1. Topical ocular decongestants

α -Adrenergic agonists help decongest and whiten the eye with the immediate onset of vasoconstriction of the conjunctival vessels. They offer little to no relief of itching. Their efficacy in AC has only been established in clinical trials in conjunction with topical antihistamines, not as a solo

treatment. However, they are readily used as over the counter medication. α -Adrenergic agonists have been known to exert tachyphylaxis and rebound hyperemia [2•, 14••].

The first topical medication approved for use in ocular allergy by the FDA was naphazoline in 1971. Other medications of the sort are tetrahydrozoline, phenylephrine, ephedrine, and brimonidine. The former appears to minimize tachyphylaxis and is in the final stages of development for the treatment of ocular redness [14••].

2. Topical antihistamines

Topical first-generation ocular antihistamines include anthazoline and pheniramine, but their use has been substituted by newer topical antihistamines more suitable for long-term use like 0.05% levocabastine and 0.05% emedastine. Levocabastine has been found to be safe and efficacious in a meta-analysis, with an effect similar to that of oral loratadine for controlling ocular itch [7••, 15]. All topical antihistamines block H_1 receptors. Side effects include sedation, irritation, and dry eye [14••].

3. Topical mast cell stabilizers

The model drug of this group is sodium cromoglycate and the group exerts its effectiveness by the inhibition of mast cell degranulation and release of histamine. Mast cell stabilization reduces the influx of monocytes, eosinophils, and neutrophils to the conjunctiva. Sodium cromoglycate has been shown to be superior to placebo and is beneficial on a regular administration. Other agents of this group are lodoxamine, pemirolast, and cromolyn [2•, 14••].

4. Topical dual-acting agents

In AC, the use of dual antihistamine plus mast stabilizer topical treatment is encouraged. Among these, ketotifen, azelastine, epinastine, and bepotastine are approved for twice-daily use; olopatadine and alcaftadine for once-daily use [14••].

In 1996, olopatadine 0.1% was the first dual-action topical agent approved by the FDA for the treatment of AC. Its effectiveness was found superior to second-generation antihistamines, both topical and oral, for controlling ocular itch. Available in presentations for once- or twice-daily use, in 2015, a new 0.7% olopatadine was introduced providing symptom relief of up to 24 h. Studies comparing olopatadine to ketotifen, epinastine, and azelastine have rated it superior and more comfortable [14••].

Alcaftadine was approved in 2010 for use in AC and is the most recent dual-action agent available. It has greater affinity for histamine H_1 and H_2 receptors than olopatadine and has also shown to have moderate affinity for H_4 receptors, which could impact eosinophil recruitment. Studies show good tolerance and little side effects. Murine models show that alcaftadine can stabilize and protect tight junctions of the conjunctival epithelium, another possible target for its efficacy [14••, 16, 17].

5. Topical non-steroidal anti-inflammatory agents (NSAIDs)

NSAIDs block the cyclooxygenase pathway and thus reduce the synthesis of prostaglandins and thromboxane. The topical agents 0.5% ketorolac, 0.1% diclofenac, 0.5% pranoprofen, and 0.03% flurbiprofen have proved to be more effective than placebo for the reduction of itching and ocular hyperemia [7••, 18]. Possible side effects are burning sensation and corneal melt. Although promising, these agents have only been approved for post-operative inflammation and not AC [14••].

6. Topical corticosteroids

Topical corticosteroids cause inhibition of phospholipase A, resulting in inhibition of prostaglandins and leukotriene synthesis. Topical ocular corticosteroids are highly effective in severe or chronic ocular allergy but are not frequently used in AC because of unwanted side effects. However, it has been described that in seasonal AC refractive to other treatments, topical corticosteroids can be carefully used as a short-term treatment [14••].

The regular use of intranasal corticosteroids has been described as a possible treatment use in AC, although the exact mechanism of action is unknown. Efficacy has been shown for various molecules: mometasone furoate, fluticasone furoate, fluticasone propionate, and budesonide [14••].

Systemic treatments for AC

1. Systemic antihistamines

Systemic antihistamines have a limited effect on AC but can be considered in patients with concomitant rhinitis or sinusitis. Frequent side effects include dry eye, which can exacerbate the symptoms and discomfort of patients with AC [14••]. Newer, second-generation oral antihistamines like loratadine and fexofenadine have been approved for the relief of symptoms of seasonal AC and can be used in children above 2 years of age [2•]. Clinical trials have demonstrated the efficacy of new oral antihistamines against placebo; however, few trials have assessed comparison between the multiple options sold in the market [7••].

2. Selective glucocorticoid receptor agonists (SEGRAs)

SEGRAs are a developing therapeutic option and could potentially become a target therapy for AC. They have been designed to target the anti-inflammatory mechanism known to corticosteroids but with reduced side effects. ZK209614 and mapracorat are examples of this novel treatment [14••, 19].

3. Kinase inhibitors

Another anti-inflammatory target being developed is kinase inhibitors. Currently, three are being developed for a potential use in AC: PRT02070, PRT02761, and PRT02607. Efficacy has yet to be determined for these [14••].

4. IL-1 receptor antagonist

IL-1 appears to play a role in the initiation and maintenance of the inflammatory cascade and potential inhibitor molecules are being studied. EBI-005 topical ophthalmic solution is being tested for the treatment of moderate to severe cases of AC [19].

5. Leukotriene receptor antagonist

As explained before, leukotrienes play a part in the AC inflammatory cascade. Montelukast is an antagonist of type I cysteinyl-leukotriene receptors currently used in asthma and rhinitis. Evidence suggests that it can improve ocular symptoms of allergic eye disease. However, it has not proven superior to oral antihistamines [19, 20].

Allergen-specific immunotherapy

Allergen-specific immunotherapy (SIT) is recommended as an alternative for patients in whom classical pharmacological management is ineffective or

poorly tolerated. It induces a decrease in the sensitivity of the conjunctiva and modifies the humoral and cellular response to allergens. Consistent evidence supports the use and safety of sublingual or subcutaneous immunotherapy in rhinoconjunctivitis. Strong evidence suggests that subcutaneous immunotherapy (SCIT) improves conjunctival symptoms in adults with AC. The evidence, although positive, is less strong for the pediatric population. SCIT may reduce the need for alternate medication. As for sublingual immunotherapy, evidence of improvement of symptoms in AC is moderate for both adults and children. SLIT is a safe and comfortable choice which may be preferred for use in children. Efficacy in relation to ocular symptoms has shown to persist years after completing the administration of SIT [7•, 19, 21].

Natural history and prognosis of AC

The NHANES III epidemiology report showed that up to 40% of patients will experience ocular symptoms at least once in their lifetime and that up to 20% of those with ocular symptoms reported these throughout each decade of life. Little more has been described of the natural history of the disease; however, it is known that younger patients present more frequently with nasal and ocular symptoms combined and that patients 50 years and older have more frequent isolated ocular complaints [1].

Disease prognosis is favorable and benign, although quality of life is affected in AC, as in other chronic allergic diseases. Complications such as conjunctival fibrosis, bacterial colonization, keratoconus, and vision loss are associated to more morbid conditions of the allergic ocular disease spectrum, such as AKC and VKC [2•].

Conclusion and future perspectives

AC plays an important role in the diverse group of type I hypersensitivity disorders and should not be overlooked. Although AC is frequently diagnosed alone, it is of primary importance to study the possible association to other allergic diseases in each individual.

The diagnosis of AC is predominantly clinical but evidence of IgE-mediated mechanisms and the possible culprit allergens should be established in all patients, to support the diagnosis and guide the therapeutic steps.

Treatment encompasses non-pharmacological and pharmacological approaches. The preferred pharmacological medications are topical dual-acting agents, which have both local antihistamine and mast cell stabilizing properties.

SIT is a possible alternative in patients with moderate to severe symptoms specially those associating other allergic comorbidities. Further investigation is needed to analyze the application of SIT in ocular allergic disease alone and to establish the optimal route of administration.

Novel pharmacological approach aims at inhibiting inflammatory pathways in a specific molecular level which prompts the need for further research not only in drug pathways but also in pathophysiological mechanisms.

As clinicians, the appropriate identification and management of ocular signs and symptoms should be carefully integrated into our everyday practice. To

achieve this, general multidisciplinary consensus should be recognized both by ophthalmological and allergic societies for the adequate definition, classification, and treatment of these patients.

Compliance with Ethical Standards

Conflict of Interest

Silvia Riggioni Víquez declares that she has no conflict of interest.

Carmen Riggioni Víquez declares that she has no conflict of interest.

Paula Ribó González declares that she has no conflict of interest.

Giovanna Araujo Sánchez declares that she has no conflict of interest.

Maria Cesarea Sánchez-Hernández declares that he has no conflict of interest.

Antonio Luis Valero Santiago declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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