Consensus Document on Allergic Conjunctivitis (DECA)

Sánchez-Hernández MC[1], Montero J[2,3*], Rondon C[4], Benítez del Castillo JM[5*], Velázquez E[6,7], Herreras JM[8*], Fernández-Parra B[9], Merayo-Lloves J[10*], Del Cuvillo A[11], Vega F[12], Valero A[13], Panizo C[14], Montoro J[15], Matheu V[16], Lluch-Bernal M[17,18], González ML[19], González R[16], Dordal MT[20,21], Dávila I[22], Colás C[23], Campo P[4], Antón E[24], Navarro A[25] (SEAIC 2010 Rhinoconjunctivitis Committee). [*] (Spanish Group Ocular Surface-GESOC)

[1]UGC Pneumology and Allergy, Complejo Hospitalario Universitario de Huelva, Huelva, Spain
[2]Department of Ophthalmology, Hospital Virgen Macarena, Sevilla, Spain
[3]Centro CARTUJA-VISIO, Sevilla, Spain
[4]UGC Allergy, IBIMA-Hospital Regional, UMA, Málaga, Spain
[5]Department of Ophthalmology, Hospital Clínico San Carlos, Universidad Complutense de Madrid, Madrid, Spain
[6]QUIRON Sagrado Corazón, Sevilla, Spain
[7]Hospital Victoria Eugenia Cruz Roja, Sevilla, Spain
[8]Department of Ophthalmology, HCUV, Valladolid, Spain
[9]Department of Allergology, Hospital El Bierzo, Ponferrada, León, Spain
[10]Instituto Oftalmológico Fernández-Vega, University of Oviedo, Oviedo, Spain
[11]Asthma and Rhinitis Unit, Department of Otorhinolaryngology, Hospital de Jerez, Cádiz, Spain.
[12]Department of Allergology, Hospital de la Princesa, Instituto de Investigación Sanitaria Princesa (IP), Madrid, Spain.
[13]Department of Pneumology and Allergy, Hospital Clínic i Universitari, Institut d´Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERES, Barcelona, Spain.
[14]Department of Allergology, Hospital Nuestra Señora del Prado, Toledo, Spain
[15]Allergy Unit, Hospital Universitario Arnau de Vilanova, Facultad de Medicina Universidad Católica de Valencia "San Vicente Mártir", Valencia, Spain
[16]Department of Allergology, Hospital del Tórax-Ofra, HUNS La Candelaria, Tenerife, Spain
[17]Department of Allergology, Hospital La Paz, Madrid, Spain
[18]Department of Allergology, Hospital Virgen del Valle, Toledo, Spain
[19]Department of Allergology, Hospital Clínico San Carlos, Madrid, Spain
[20]Department of Allergology, Hospital Municipal de Badalona, Badalona, Spain
[21]Department of Allergology, Sant Pere Claver Fundació Sanitària, Barcelona, Spain
[22]Department of Allergology, Hospital Universitario, IBSAL, Salamanca, Spain
[23]Department of Allergology, Hospital Clínico Universitario, Zaragoza, Spain
[24]Department of Allergology, Hospital Universitario Marqués de Valdecilla, Santander, Spain
[25]UGC of Allergology Sevilla, Hospital El Tomillar, Sevilla, Spain

Abstract

Allergic conjunctivitis (AC) is an inflammatory disease of the conjunctiva caused mainly by an IgE-mediated mechanism. It is the most common type of ocular allergy. Despite being the most benign form of conjunctivitis, AC has a considerable effect on patient quality of life, reduces work productivity, and increases health care costs. No consensus has been reached on its classification, diagnosis, or treatment. Consequently, the literature provides little information on its natural history, epidemiological data are scarce, and it is often difficult to ascertain its true morbidity. The main objective of the Consensus Document on Allergic Conjunctivitis (***D****ocumento d****E*** *Consenso sobre* ***C****onjuntivitis* ***A****lérgica* [DECA]), which was drafted by an expert panel from the Spanish Society of Allergology and Spanish Society of Ophthalmology, was to reach agreement on basic criteria that could prove useful for both specialists and primary care physicians and facilitate the diagnosis, classification, and treatment of AC. This document is the first of its kind to describe and analyze aspects of AC that could make it possible to control symptoms.

Key words: Allergic conjunctivitis. Ocular allergy classification. Allergic conjunctivitis diagnosis. Allergic conjunctivitis treatment. Allergic disease control.

Resumen

La conjuntivitis alérgica (CA), es una enfermedad inflamatoria que se produce en la conjuntiva ocular mediada predominantemente, por un mecanismo IgE. En la alergia ocular, la CA se considera la entidad más frecuente y, a pesar de ser la forma más benigna, supone para los pacientes una importante afectación en su calidad de vida, una disminución de su productividad laboral y un elevado gasto sanitario. En la actualidad, no existen criterios consensuados acerca de su clasificación, diagnóstico y tratamiento de tal manera que por los trabajos publicados es difícil conocer su historia natural, existen escasos datos sobre su epidemiologia y, a veces es complejo identificar su morbilidad real. El objetivo principal del ***D****ocumento d****E*** *Consenso sobre* ***C****onjuntivitis* ***A****lérgica* (DECA) realizado por un grupo de expertos de las Sociedades Españolas de Alergología y Oftalmología, ha sido establecer de forma consensuada unos criterios básicos que puedan ser útiles tanto para los especialistas, como para los médicos de atención primaria y que faciliten el diagnóstico, la clasificación y el tratamiento de los pacientes con CA. Por primera vez se describen y analizan distintos aspectos que pueden servir de herramientas para establecer el control de los síntomas de la CA.

Palabras clave: Conjuntivitis alérgica. Clasificación alergia ocular. Diagnóstico conjuntivitis alérgica. Tratamiento conjuntivitis alérgica. Control enfermedades alérgicas.

Introduction

Ocular symptoms suggestive of allergy are a common presenting complaint in both adults and children in ophthalmology, allergology, and primary care. The US National Health and Nutrition Examination (NHANES III) study revealed that 40% of the population had had ocular symptoms suggestive of allergy during the previous 12 months [1]. In the Alergológica 2005 study, which was performed in allergology departments throughout Spain, 34.8% of 5000 patients attended the clinic because of ocular symptoms, which were the second most common reason for visiting an allergy specialist [2].

Ocular allergy encompasses a group of diseases with different immunopathological mechanisms, clinical manifestations, and responses to treatment. No unanimously agreed definition has been reached, because the definition criteria have not always been uniform. In 2006, for example, the International Ocular Inflammation Society [3] proposed a classification based on clinical aspects and immunopathologic mechanisms (Table 1), and in 2012, Leonardi et al [4] published a new classification based on pathophysiology and hypersensitivity mechanisms (Figure 1).

It is widely accepted that an IgE-mediated mechanism is involved in conditions such as vernal keratoconjunctivitis, atopic keratoconjunctivitis, and allergic conjunctivitis (AC). Other, more complex immunopathologic mechanisms are also involved in vernal keratoconjunctivitis and atopic keratoconjunctivitis. In the former, inflammation seems to be caused mainly by T cells, eosinophils, and cytokines (T_H2), while in the latter, T cells also participate in the inflammatory process, although the increase in IFN-γ levels suggests that the response is mainly T_H1-mediated [5].

AC results from a predominantly IgE-mediated inflammatory reaction in the conjunctiva. Since it usually occurs alongside other allergic diseases, mainly rhinitis, the term *rhinoconjunctivitis* is often used interchangeably to refer to both entities.

The present ***D****ocumento d****E*** *Consenso sobre* ***C****onjuntivitis* ***A****lérgica* (Consensus Document on Allergic Conjunctivitis, or DECA) was drawn up by ophthalmologists from the Spanish Ocular Surface and Cornea Group (GESOC) and allergologists from the Rhinoconjunctivitis Committee of the

Table 1. Clinical and Immunopathological Classification of Ocular Allergy

	IgE-Mediated	IgE-Mediated and Non-IgE-Mediated	Non-IgE-Mediated
Intermittent	SAC		
Persistent	PAC	VK	GPC
Chronic		AK	CDC

Source: Adapted from Leonardi et al [3].
Abbreviations: AK, atopic keratoconjunctivitis; CDC, contact dermatoconjunctivitis; GPC, giant papillary conjunctivitis; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; VK, vernal keratoconjunctivitis.

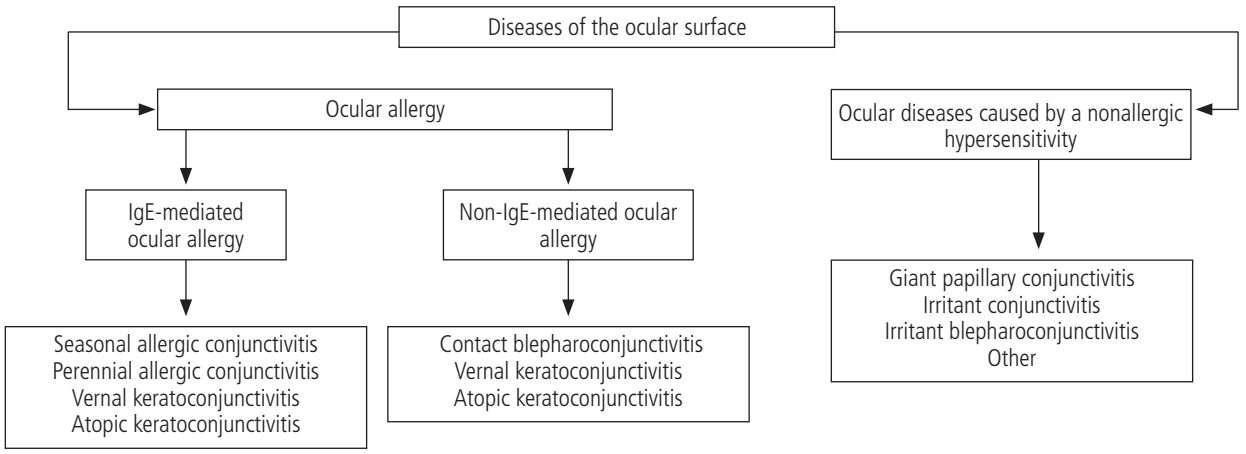

Figure 1. Diseases of the ocular surface caused by a hypersensitivity mechanism [4].

Spanish Society of Allergology and Clinical Immunology. It was designed to establish consensus on various aspects of AC. In particular, it addresses the classification, clinical manifestations, monitoring, and treatment of the disease with the aim of improving evaluation, management, and control.

Methods

The DECA consensus document aims to provide a structured, scientific update on AC based on a review of the available literature and on expert consensus reached by a panel comprising members of the Spanish Society of Allergology and the Spanish Society of Ophthalmology.

The document takes the form of a narrative review that presents the most relevant scientific evidence on the symptoms, diagnosis, and treatment of AC.

A systematic review of the literature spanning the last 10 years was performed using the MEDLINE (National Library of Medicine) and EMBASE (Elsevier Science) databases with the following search terms: "ocular allergy," "classification of allergic conjunctivitis," "diagnosis and allergic conjunctivitis," "differential diagnosis and ocular allergy," "treatment of allergic conjunctivitis," "quality of life and allergic diseases," and "control of allergic diseases." The experts reviewed meta-analyses, systematic reviews, case-control studies, observational studies, and case reports on AC. Expert opinions and personal experiences of the panel members were also taken into account. The recommendations were graded according to the Scottish Intercollegiate Guidelines Network scale, proposed by Harbour and Miller [6] (Table 2).

When scientific evidence was insufficient, doubts were discussed and decisions were taken based on questionnaires with specific responses in order to agree on the most adequate approach from the point of view of the authors. The final version of the document was agreed upon and reviewed by all the authors.

Classification of AC

As with allergic rhinitis, AC has traditionally been classified according to the time of the year at which the patient is exposed to the allergen, with 2 categories: seasonal AC, which is triggered mainly by exposure to pollens, and perennial AC, which affects sensitized persons exposed to dust mites, molds, animal dander, and occupational allergens [7].

However, this classification cannot be applied to all patients and is confusing for several reasons. On the one

Table 2. Grades of Recommendation of the Scottish Intercollegiate Guidelines Network

Grade of Recommendation	Level of Evidence
A	At least one meta-analysis, systematic review, or randomized clinical trial rated as 1++ and directly applicable to the target population or a systematic review of randomized clinical trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+

Source: Harbour and Miller [6]. For more information, see http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html

hand, some pollens are more or less perennial, depending on the geographic area, and allergens considered perennial according to environmental conditions may not induce symptoms throughout the year. On the other hand, as occurs with bronchial epithelial cells [8] and nasal epithelial cells [9], exposure to environmental irritants, in particular, diesel particles, can increase expression of adhesion molecules and production of cytokines in the conjunctival epithelium [10]. This allergic inflammatory response and its accompanying perennial ocular symptoms can mask the "seasonality" of some allergens.

Proposed Classification

Given the common association between conjunctivitis and allergic rhinitis, we believed it necessary to harmonize the classification criteria for both entities based on *1*) the Allergy and its Impact on Rhinitis (ARIA) document [11] and the classification criteria of Valero et al [12] for allergic rhinitis (grade of recommendation B) adapted to AC and *2*) the AC classification system proposed by Leonardi et al [4] (grade of recommendation D), which takes account of the frequency and severity of ocular signs and symptoms. Thus, the classification set out in the present consensus document, which has yet to be validated, considers AC as *intermittent* when it involves ocular signs and symptoms (pruritus, tearing, photophobia, and hyperemia) for a maximum of 4 days a week or a maximum of 4 consecutive weeks, and as *persistent* when ocular symptoms are present for more than 4 days a week and for more than 4 consecutive weeks. As for severity, we propose that AC should be considered *mild* when signs and symptoms are not bothersome, do not affect vision, and do not hamper occupational or academic tasks/activities of daily living, reading, and/or sport; as moderate when between 1 and 3 of these conditions are met; and as *severe* when all of these conditions are met (Figure 2).

Diagnosis of AC

Diagnosis of AC is based on a family and personal history of atopy, characteristic clinical signs and symptoms, and results of appropriate additional tests [4] (grade of recommendation D).

Patients may have a clinical history suggestive of AC at any age, regardless of sex. AC often co-occurs with rhinitis (in 66% of adults [13] and up to 97% of children [14]), asthma (in 16% of adults [15] and 56% of children [14]), and atopic dermatitis (in 25%-42% of adults [16] and 33% of children [14]). AC generally affects both eyes, and patients report symptoms such as conjunctival pruritus (main symptom) [17], tearing, and a burning sensation. Blurred vision and photophobia can occur in the most severe cases. Blurred vision in AC is usually caused by altered composition and stability of the tear film and has been shown to affect more than 78% of patients assessed using interferometry [18].

The clinical signs can be assessed by slit lamp examination. If this is not possible, a light source combined with fluorescein staining can be used when abnormalities of the epithelial cells of the ocular surface are suspected. Mild to moderate hyperemia can be observed on the conjunctiva (conjunctival injection), as can edema (chemosis), which is usually moderate in severity. The eyelids are frequently edematous, and the palpebral conjunctiva pale pink in appearance. In some cases, diffuse areas of slight papillary hypertrophy can be observed in the upper palpebral conjunctiva. The discharge is aqueous or mucoid, and the cornea is not usually affected [19].

Diagnosis is confirmed by positive results in skin tests with suspect allergens or serum specific IgE to whole allergens or their purified molecular components [4]. The results of skin tests and/or specific IgE testing are not always conclusive, since up to 24% of patients may be sensitized to multiple allergens [20]. Moreover, in some cases of AC, skin test results are negative, especially if there is no association with rhinitis [21]. Levels of free specific IgE, total IgE, cytokines, and inflammatory markers (eg, eosinophil cationic protein) can

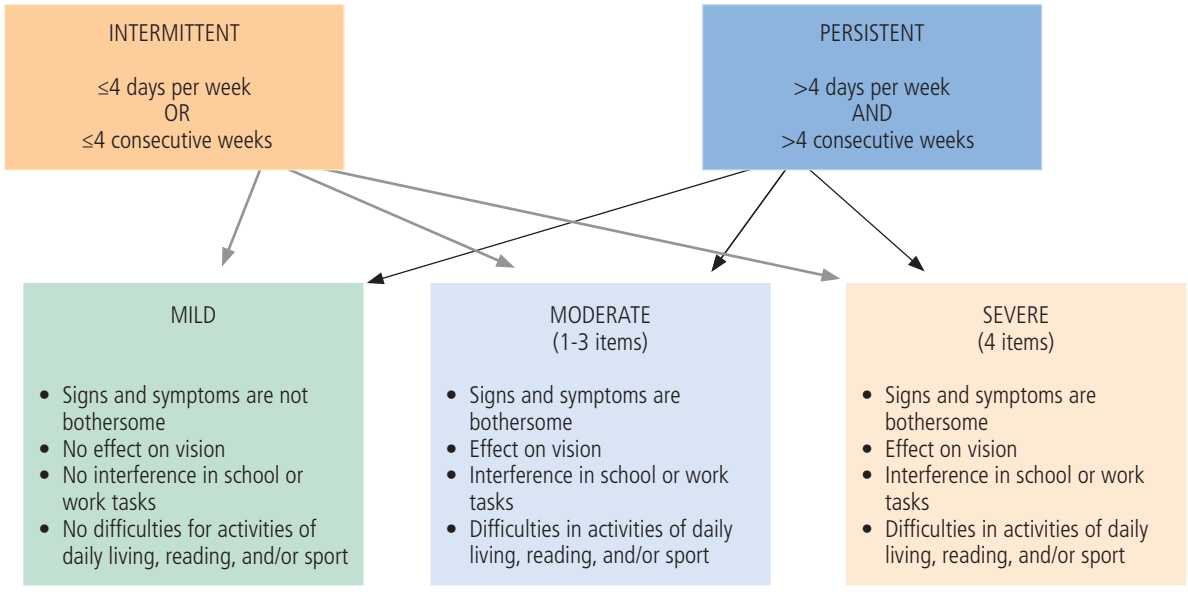

Figure 2. Classification of allergic conjunctivitis proposed in the Consensus Document on Allergic Conjunctivitis (DECA) (grade of recommendation D).

be measured in tear fluid. Conjunctival cytodiagnosis is also an option, but it is not useful in daily clinical practice and is more suited to research [22].

Other criteria to support a diagnosis of AC include response to topical antihistamines and/or mastocyte stabilizers [23] (grade of recommendation A).

In order to confirm the etiologic diagnosis of AC, it may sometimes be necessary to perform a conjunctival challenge test, which can confirm the reactivity of the allergen in the conjunctiva of patients with positive skin test results. However, the challenge test is particularly useful in patients with negative skin tests or serum specific IgE determinations and a clinical history suggestive of AC, since it can be used to assess the local and specific response of the conjunctiva. Similarly, an ocular challenge can help in the diagnosis of patients sensitized to multiple allergens and in certain patients with occupational allergy [24].

Differential Diagnosis of AC

The differential diagnosis of AC can be challenging because of the wide range of disorders that mimic or mask this disease. The first steps in diagnosis are a clinical history and evaluation of environmental risk factors.

Table 3 shows some specific characteristics that can provide valuable clues to facilitate the diagnosis of AC.

Table 3. Diseases of the Ocular Surface. Keys to Differential Diagnosis (Grade of Recommendation D)

	AC	VK	AK	GPC	CBC	KS
Family history	Frequent	Possible	Constant	Possible	Possible	No
Association with other atopic diseases	Rhinitis Asthma	Variable	Dermatitis Asthma Rhinitis	Variable	Variable	No
Age group	Children/ Adults	Children	Adults	Adolescents/ Adults	Adults	Adults
Sex	No predominance	Male	Male	No predominance	No predominance	Female
Season	Spring/ Perennial	Perennial/ Summer	Perennial	No	No	No
Exposure to topical agents	No	No	No	No	Yes	Yes
Contact lenses	No	No	No	Yes	No	No
Ocular pruritus	Present	Intense	Present	Present	Present	Variable
Conjunctival hyperemia	Present	Present	Present	Present	Present	Variable
Photophobia	Frequent	Intense	Constant	Constant	Variable	Variable
Discharge	Watery	Mucous	Variable	Mucous	Variable	None
Palpebral involvement	Edema	Edema				
Pseudoptosis	Dermatitis	Edema	Dermatitis	No		
Corneal involvement	No	Yes	Yes	No	No	Yes
Papillary hypertrophy	No	>1 mm (limbus affected)	<1 mm	0.3-1 mm	No	No
Visual discomfort	Minimal	Mild	Severe	Minimal	Minimal	Variable
Total serum IgE	High	Variable	Very high	Variable	Variable	Normal
Skin test/serum specific IgE	Positive	Variable	Positive	Variable	Variable	Negative
Eosinophils in corneal scrape	Frequent	Typical	Typical	Frequent	No	No
Conjunctival sickle cells	Increased	Increased	Reduced	Variable	Variable	Reduced
Response to antihistamines and/or topical mast cell stabilizers	Typical	Low	Low	Variable	No	No
Response to topical corticosteroids	Constant	Constant	Constant	Constant	Constant	Constant

Source: Adapted from Mantelli et al [25].
Abbreviations: AC, allergic conjunctivitis; AK, atopic keratoconjunctivitis; CBC, contact blepharoconjunctivitis; GPC, giant papillary conjunctivitis; KS, keratoconjunctivitis sicca; VK, vernal keratoconjunctivitis.

Proposal for Diagnosis

Based on our literature review for the DECA, we propose criteria for clinical suspicion that can be used by both primary care physicians and specialists (grade of recommendation D). Nevertheless, large-scale, prospective, and randomized studies are necessary to validate these criteria (Table 4).

Once a suspicion of AC has been raised, and following the diagnostic plan proposed by Leonardi et al [4], we recommend confirmation using an allergy workup based on skin tests, determination of serum specific IgE, and/or a conjunctival challenge test (grade of recommendation D).

Treatment of AC

The first objective when treating AC consists of avoidance or minimization of contact between the allergen and the conjunctiva by means of a series of nonpharmacologic measures. If the allergic inflammatory process is triggered in the conjunctiva, the characteristic signs and symptoms of AC that appear can be treated with pharmacologic measures, such as antihistamines, membrane stabilizing agents, multiple action drugs, vasoconstrictors, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. An alternative approach, specific immunotherapy, attempts to suppress or regulate the immune response triggered by the allergen in sensitized individuals and thus not only intervenes in the control of symptoms, but also modifies progression of the allergic disease (Table 5).

Nonpharmacologic Measures [26] (Grade of Recommendation A)

As with any allergic disease, general environmental measures are recommended and include specific actions to reduce exposure to house dust mite, molds, animal dander, and pollen.

Other nonpharmacologic interventions are applied cold (eg, compresses soaked in water, preservative-free artificial tears, and saline solution) and act by washing allergens from the conjunctiva and constricting the conjunctival vessels, thus relieving edema and hyperemia. Large wraparound sunglasses can be used to prevent contact with aeroallergens and improve photophobia.

When combined with appropriate information and patient education, these measures can achieve improved disease control.

Table 4. Clinical Criteria for Suspicion of Allergic Conjunctivitis Proposed in the Consensus Document on Allergic Conjunctivitis (DECA) (Grade of Recommendation D)

Bilateral Conjunctival Hyperemia and Pruritus (Together With at Least 3 of the Criteria Below)
1. Ocular symptoms associated with exposure to suspicious allergens [17]
2. Association with other allergic diseases (rhinitis, asthma, atopic dermatitis) [17]
3. Response to topical pharmacologic therapy (antihistamines, mast cell stabilizers, dual action agents) [23]
4. Absence of giant papillary conjunctivitis [19]
5. Absence of corneal involvement [19]

Table 5. Treatment in Allergic Conjunctivitis [7]

Nonpharmacologic	Avoid allergens Cold compresses Artificial lubricants	
Pharmacologic		
Ocular topical	Antihistamines	Antazoline, emedastine, levocabastine, pheniramine
	Vasoconstrictors	Naphazoline, oxymetazoline, phenylephrine, tetrahydrozoline
	Mast cell stabilizers	Nedocromil, lodoxamide, sodium cromoglycate, spaglumic acid
	NSAIDs	Diclofenac, flurbiprofen, ketorolac
	Dual action agents	Azelastine, epinastine, ketotifen, olopatadine
	Corticosteroids	Betamethasone, dexamethasone, fluorometholone, loteprednol, medrysone, prednisolone, rimexolone
Oral	Antihistamines	Bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, rupatadine
Nasal topical	Corticosteroids	Fluticasone, mometasone
Specific immunotherapy: Subcutaneous, sublingual		

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

Pharmacologic Therapy

Systemic antihistamines block ocular symptoms induced by histamine and interaction with H_1 receptors in nerve endings (mainly through relief of the sensation of pruritus). Some antihistamines are thought to have anti-inflammatory effects, such as inhibition of expression of intercellular adhesion molecules (ICAM-1) and effects on platelet-activating factor (PAF) [27,28].

First-generation antihistamines are not recommended because of their sedative effect and anticholinergic activity. Second-generation antihistamines (bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, mizolastine, and rupatadine) have similar efficacy but a more manageable sedation profile and fewer adverse effects [11] (grade of recommendation B). Antihistamine drugs are usually administered to control nasal and ocular symptoms in patients with rhinoconjunctivitis. However, keratoconjunctivitis sicca has been reported with oral antihistamines whose antimuscarinic activity causes tear film abnormalities [29]. These alterations in the conjunctival epithelium can increase the inflammatory response to the allergen [30].

First-generation topical ocular antihistamines (antazoline and pheniramine) are available over the counter, although they are poorly tolerated, their effect is short-lasting, and their potency is limited [22] (grade of recommendation D). They are often combined with vasoconstrictors to increase duration of effect.

Second-generation topical antihistamines (levocabastine and emedastine) have a longer half-life (4-6 hours) and a good safety and efficacy profile, even in children [31,32] (grade of recommendation A). When symptoms are mainly ocular, topical antihistamines are preferred over oral drugs because of their faster onset of action. Combining topical and oral antihistamines increases efficacy with respect to oral treatment only [22,31] (grade of recommendation B).

Mast cell stabilizers (lodoxamide 0.1%, nedocromil 2%, sodium cromoglycate 2% and 4%, spaglumic acid 4%) inhibit mastocyte degranulation [33], thus leading to blockade of preformed mediator release and activation of the arachidonic acid cascade. Since these agents have to be administered every 6 to 8 hours for at least 2 weeks, adherence is usually poor [23] (grade of recommendation A).

Dual-action agents (azelastine, epinastine, ketotifen, and olopatadine) have the advantage that they act as mast cell stabilizers and selective H_1 receptor antagonists (olopatadine and ketotifen). Some, such as epinastine, act on both H_1 receptors (by reducing pruritus) and H_2 receptors (by reducing vasodilation), while others, such as azelastine, also reduce expression of ICAM-1 and inhibit PAF activity. These agents act quickly with a lasting effect, probably because of their ability to suppress the release of mediators and inhibit the recruitment of inflammatory cells [34]. They are administered every 12 hours and have proven more efficacious than fluorometholone in SAC [35] (grade of recommendation A).

Vasoconstrictors (naphazoline, oxymetazoline, phenylephrine, tetrahydrozoline) are α-adrenergic agonists that relieve the reddening caused by conjunctival vasodilation. Their efficacy is reduced with other symptoms, their duration is short (≤2 hours), and tolerance is poor. In addition, rebound hyperemia and tachyphylaxis limit combination with other allergy drugs. Neither long-term nor AC-specific use is recommended, and the drugs should be administered with caution in patients with glaucoma, hyperthyroidism, or cardiovascular disease [34] (grade of recommendation D).

Ophthalmic NSAIDs (diclofenac 0.1%, flurbiprofen 0.03%, and ketorolac 0.5%) act by blocking the cyclooxygenase pathway and, therefore, synthesis of prostaglandins and thromboxanes. These drugs have proven efficacy against conjunctival hyperemia and pruritus [36] (grade of recommendation A). Ketorolac is approved for the treatment of AC, but in comparative studies it has been seen to be less effective than olopatadine and emedastine [37]. Application of NSAIDs is limited due to a stinging and burning sensation on topical administration.

Nasal corticosteroids are not considered a first-choice treatment for AC, but they can improve ocular symptoms by diminishing the nasal-ocular reflex in patients who also have rhinitis. In particular, mometasone furoate [38] and fluticasone furoate [39] can relieve the symptoms of allergic rhinoconjunctivitis (grade of recommendation A). Prolonged use over several months does not seem to generate a significant risk of ocular hypertension or glaucoma, although limited data have been reported [40]. As for efficacy in controlling ocular symptoms, no preference has been established between intranasal corticosteroids and oral antihistamines in patients with allergic rhinoconjunctivitis [41].

Antileukotrienes (mainly montelukast) are included in the ARIA guidelines as a possible treatment for the nasal symptoms of allergic rhinoconjunctivitis, since they block the activity of leukotrienes (lipid mediators). The role of antileukotrienes in the control of ocular symptoms in AC has been reviewed in a meta-analysis [42], which showed that montelukast was more effective than placebo in seasonal AC, but less effective than oral antihistamines in adult patients (grade of recommendation A).

Ocular corticosteroids are the most potent anti-inflammatory agents because they interfere with intracellular protein synthesis and cause blockade of phospholipase A2, the enzyme responsible for the formation of arachidonic acid. These drugs also act by inhibiting production of cytokines and migration of inflammatory cells. Ocular corticosteroids are not considered first-choice therapy for AC, although less potent drugs, the so-called *soft corticosteroids* (eg, fluorometholone, medrysone, loteprednol and rimexolone) are used to treat moderate inflammation. When inflammation is severe, the drugs of choice are betamethasone, dexamethasone, and prednisolone [37] (grade of recommendation B). The lowest doses possible should be administered over short periods in all cases. The potential adverse effects (increased intraocular pressure, formation of cataracts, and viral, bacterial, and fungal infections) mean that patients have to be strictly monitored by an ophthalmologist.

Immunotherapy

The World Health Organization recommends allergen-specific immunotherapy as an effective approach in patients with allergic diseases such as rhinoconjunctivitis and asthma.

Both sublingual and subcutaneous administration seem to be able to induce tolerance in the short and long term via the same mechanism: high doses of allergen induce a deviation of the immune response in favor of T_H1 lymphocytes, with release of IFN-γ and production of regulatory T cells. Both play a key role in the secretion of IL-10 and transforming growth factor β, which in turn suppress the allergen-specific T_H2 response [43].

Ocular symptoms improve in patients with allergic rhinoconjunctivitis receiving specific immunotherapy [4,44], even after discontinuation of treatment [45]. When immunotherapy is analyzed in terms of the patients who receive it, ocular symptoms are relieved both overall and by type of patient (>40% in the case of pruritus), and less medication is consumed (reduction of 63%) in patients with rhinoconjunctivitis or seasonal AC, but not in patients with perennial AC [46,47] (grade of recommendation A).

Few studies have assessed changes in sensitivity to the allergen using a conjunctival challenge before and after immunotherapy, but in all cases, the sensitivity threshold increased [46] (grade of recommendation A).

The US Agency for Healthcare Research and Quality published a systematic review of the results of randomized controlled studies carried out in patients (adults and children) with rhinoconjunctivitis and/or allergic asthma treated with sublingual and subcutaneous immunotherapy. Despite variations due to methodological bias, the analysis of the efficacy of immunotherapy in AC showed that subcutaneous immunotherapy relieves ocular symptoms. Evidence was strong for adults (grade of recommendation A) but weak for children and adolescents. Evidence for sublingual immunotherapy is moderate for both adults and children [48].

Monoclonal Antibodies

Omalizumab is a humanized IgG antibody that binds to free IgE and prevents it from interacting with the high-affinity receptor (FcεRI) on the surface of the mast cell, thus inhibiting the inflammatory cascade triggered by degranulation of the mast cell.

Although significant relief of ocular symptoms has been observed with omalizumab in patients with seasonal rhinitis caused by allergy to Japanese cedar pollen [49] (grade of evidence B), the drug has not been authorized for the treatment of AC.

Proposal for Treatment

Based on available therapeutic approaches for AC, we propose a treatment algorithm (Figure 3) that has yet to be validated (grade of recommendation D).

The indication for pharmacologic and nonpharmacologic measures and for immunotherapy is addressed in a stepwise

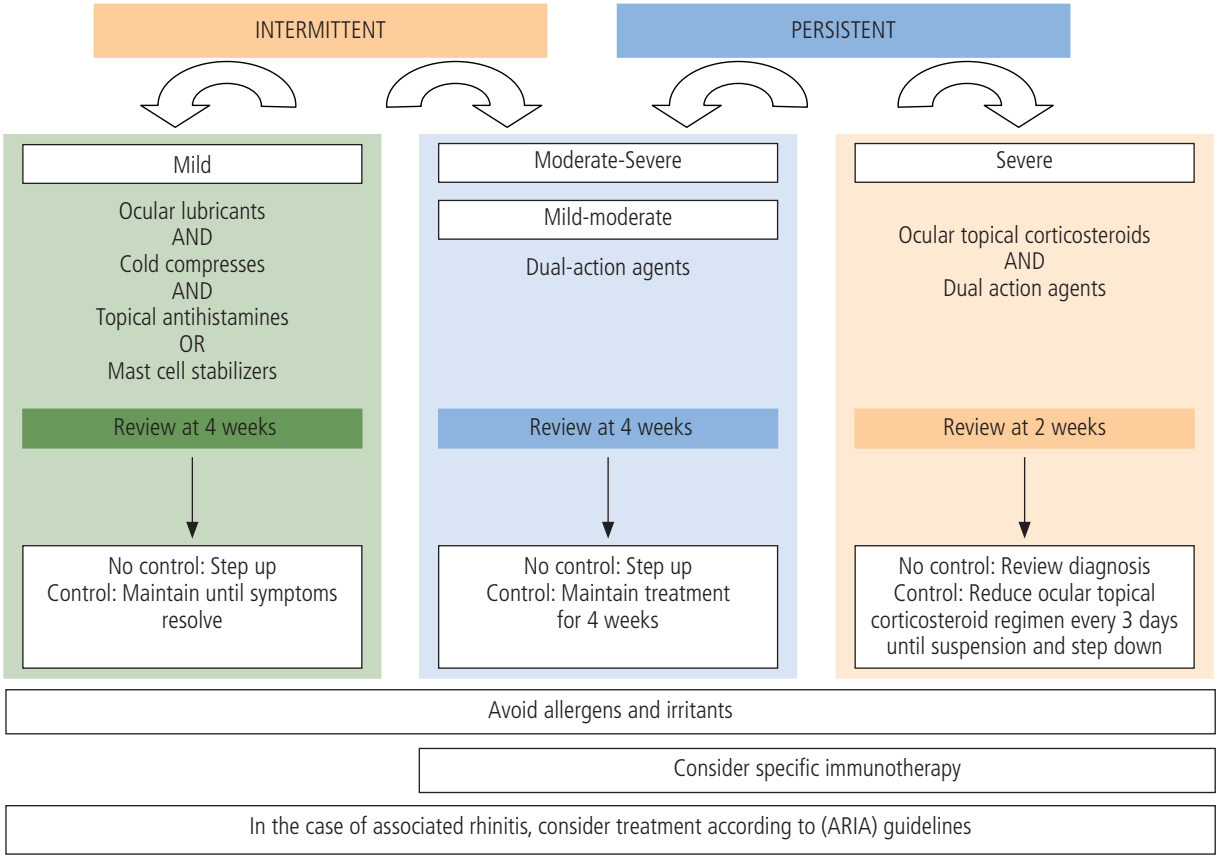

Figure 3. Treatment of allergic conjunctivitis proposed in the Consensus Document on Allergic Conjunctivitis (DECA) (grade of recommendation D).

fashion, alongside the classification for AC proposed above.

At any stage of AC, avoiding exposure to both the allergens responsible for conjunctivitis and nonspecific irritants is considered a useful measure.

It is important to explore the presence of associated rhinitis and to evaluate combined treatment (oral antihistamines and antileukotrienes). Intranasal corticosteroids are a useful option for relief of nasal and ocular symptoms, although they are not shown in Figure 3 in order to simplify the algorithm.

We propose specific immunotherapy from the onset of AC, particularly when it is associated with rhinitis, except in patients with intermittent-mild AC.

We believe that 4 weeks is the optimal point at which to reevaluate response to treatment, except in the case of ocular corticosteroids, which requires a shorter interval (2 weeks) because of the potential adverse effects.

Evaluation of the Control of Allergic Conjunctivitis

Control is defined as a state of illness in which clinical manifestations are absent or have almost completely resolved with therapy. The patient has either no symptoms or symptoms that are no longer considered bothersome. Disease is partially or poorly controlled as the frequency and severity of symptoms progress. Knowledge of the degree of symptom control is a very useful tool when deciding on diagnosis and therapy.

In some allergic diseases, such as asthma, current guidelines provide criteria for evaluating control, such as the presence of symptoms, the need for rescue medication, lung function, and the presence of exacerbations [50]. Asthma control questionnaires (Asthma Control Test, Asthma Control Questionnaire) [51,52] have been validated in Spain [53,54] and have proven useful for assessing asthma control.

Disease control questionnaires can also be used in allergic rhinitis (Rhinitis Control Assessment Test, Control of Allergic Rhinitis and Asthma Test) [55], although these have not been validated in Spanish. Control of nasal symptoms has been evaluated using a visual analog scale (VAS) [56], which was compared with symptom scoring and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) using the ocular symptoms domain (E-RQLQ) (not adapted to Spain). On a scale of 0 to 10 cm, the patient marks a total score for nasal symptoms; the authors consider that allergic rhinitis is controlled when the scale is marked below 5 cm and not controlled when the scale is marked at 5 cm or above.

Specific rhinoconjunctivitis quality of life questionnaires have been validated in Spain and include the RQLQ [57] and ESPRINT-15 [58]. However, they have not yet been used to evaluate control of AC independently of allergic rhinitis. The same is true of the VAS associated with the score for ocular symptoms. Furthermore, there are no specific quality of life questionnaires for monitoring patients with AC.

The search for objective criteria that could prove useful for evaluating control of AC should include the degree of conjunctival hyperemia. Evaluation of this condition is highly variable on the part of both the observer and the patient. In the case of patients, variability arises mainly from differences in proliferation and distribution of vessels in the conjunctiva and differences in the reactivity of the vessels to environmental stimuli such as wind or tobacco smoke [59]. In the case of clinicians, interobserver variability has been minimized by the use of photographic or drawn scales that are representative of the different degrees of conjunctival hyperemia and the application of image processing techniques [60,61]. The Efron hyperemia scale for evaluation of bulbar hyperemia [62] is one of the most widely used and easily interpreted validated quantitative scales (Figure 4).

Proposal for Control

Based on the analysis of several control criteria proposed for various allergic diseases, we propose for the first time that the degree of clinical control of AC should be evaluated using the DECA criteria (grade of recommendation D). AC is classified as controlled or uncontrolled (Table 6) based

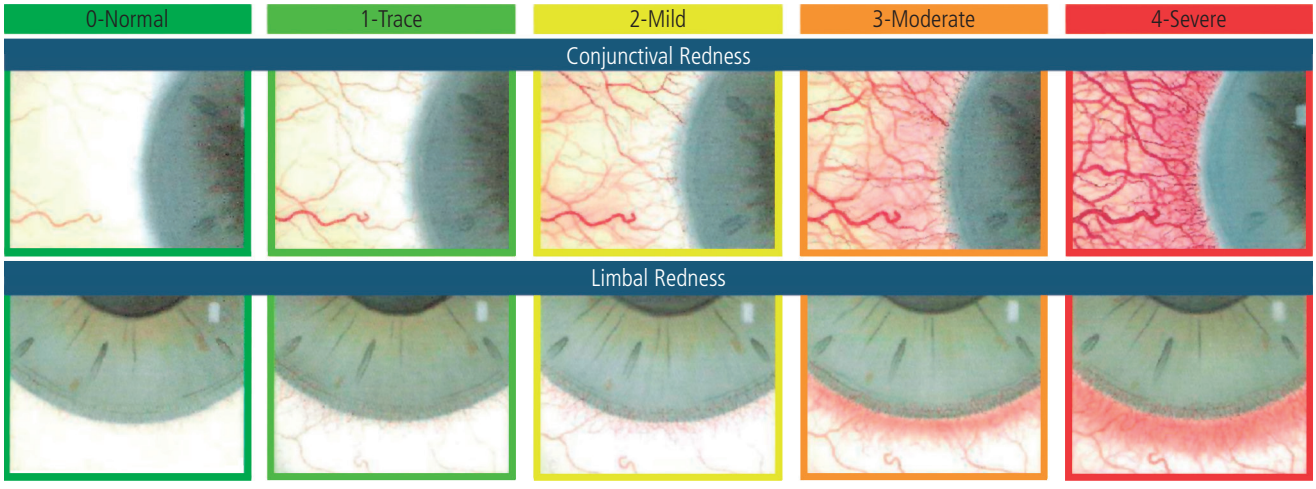

Figure 4. Efron scale [62].

Table 6. Evaluation of the Degree of Clinical Control of Allergic Conjunctivitis, as Proposed in the Consensus Document on Allergic Conjunctivitis (DECA) (Grade of Recommendation D)

	Controlled (All of the Following)	Uncontrolled (At Least 1 of the Following)
Symptoms Pruritus Tearing Visual discomfort	No symptoms or No bothersome symptoms or ≤2 d/wk	Any intensity if present >2 d/wk
Visual analog scale	<5 cm	≥ 5 cm
Hyperemia (Efron scale)	0-1	2-4

on 3 evaluation criteria: the presence and frequency of ocular symptoms, VAS score, and the degree of conjunctival hyperemia. Control criteria are evaluated at the visit to the physician and during the previous 2 weeks. They include evaluation of subjective symptoms, VAS score, and degree of conjunctival hyperemia according to the Efron scale.

- Subjective symptoms: Pruritus, tearing, and visual discomfort and frequency thereof (number of days a week). We believe that AC is controlled when the patient does not present symptoms (pruritus, tearing, or visual discomfort), when the symptoms are not bothersome, or when they occur at most 2 days a week. We consider AC to be uncontrolled if the ocular symptoms, irrespective of intensity, are present for more than 2 days a week.
- VAS: Following the description by Bousquet et al [56], control of allergic rhinitis is determined by asking the patient to score on a VAS (0-10 cm) the answer to the following question: When are your eye symptoms bothersome? We consider AC to be controlled if the mark is below 5 cm and uncontrolled if it is higher.
- Degree of conjunctival hyperemia: Depending on the degree of hyperemia during the eye examination, we consider AC to be controlled if the degree of hyperemia on the Efron scale is 0 or 1 and uncontrolled if it is between 2 and 4.

These criteria have yet to be validated in daily clinical practice using a study with a wide population base.

In conclusion, the DECA consensus document presents a new approach to the management of AC based on diagnostic criteria agreed on for the first time by an expert panel comprising ophthalmologists and allergologists. We propose a clinical classification of AC that is consistent with that of allergic rhinitis and a stepwise treatment system in line with the clinical stages of AC set out above. Using both subjective and objective tools, we establish response to treatment as the degree of disease control.

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Conflicts of Interest

Dr Sanchez-Hernández has received lecture fees from GSK, Allergy Therapeutics, Stallergenes, and ALK and has participated on advisory boards for ALK and Merck. Dr. Ignacio Dávila has received lecture fees from Stallergenes and Leti and has participated on advisory boards for Stallergenes and Faes Farma. He has also served as a consultant to Novartis and received research grant support from Thermo Fisher and Diater. Dr. Francisco Vega has received lecture fees from GSK, Chiesi, and Faes Farma. Dr. Antonio Valero has received lecture fees from Chiesi, GSK, and Stallergenes and has participated on advisory boards for Faes Farma, Meda, and Stallergenes. Dr. Carlos Colás Sanz has received lecture fees from Menarini, GSK, and AstraZeneca and has participated on advisory boards for Meda. Dr. Ana M. Navarro Pulido has received lecture fees from ALK, GSK, Leti, and Stallergenes and has participated on advisory boards for ALK, Leti, Meda, and Merck. Dr. Javier Montoro has received lecture fees from Stallergenes, GSK, and ALK and has participated on advisory boards for Faes Farma. Dr. Maria Luisa Gonzalez Gutierrez has worked as a consultant for and received funding for immunotherapy studies from Merck Laboratory. She has also received lecture fees from GSK, Pfizer, and Shire. Dr. Carmen Rondón has received lecture fees from ALK and MSD and has received training fees from GSK. Dr. Alfonso del Cuvillo has received lectures fees from Chiesi, MEDA, FAES FARMA, ALK-Abello, MSD, and Novartis and has participated on advisory boards for MEDA and Faes Farma. The remaining authors declare that they have no conflicts of interest.

Previous Presentation

Preliminary data were presented in part at the XI Reunión Anual del Grupo Español de Superficie Ocular y Cornea (GESOC) in Seville, Spain in 2013.

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María Cesárea Sánchez-Hernández

Unidad de Gestión Clínica de Neumología y Alergia
Complejo Hospitalario Universitario de Huelva
Huelva, Spain
E-mail: mcesar.sanchez@hotmail.es