ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Latin American Guideline on the Diagnosis and Treatment of Ocular Allergy – On behalf of the Latin American Society of Allergy, Asthma and Immunology (SLAAI)

Diretriz Latino-americana sobre o Diagnóstico e Tratamento da Alergia Ocular – Em nome da Sociedade Latino-americana de Alergia, Asma e Imunologia (SLAAI)

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ABSTRACT

Ocular allergy, also known as allergic conjunctivitis, is an immunoglobulin E-mediated hypersensitivity reaction of the eye triggered by airborne allergens, primarily house dust mites and grass pollen. Symptoms usually consist of ocular or periocular itching, watery eyes, and red eyes that may be present year-round or seasonally. Ocular allergy has a high frequency, is underdiagnosed, and can be debilitating for the patient. It is potentially harmful to vision in cases of severe corneal scarring, and in most patients, it is associated with other allergic conditions, especially rhinitis, asthma, and atopic dermatitis. It is classified as perennial allergic conjunctivitis, seasonal allergic conjunctivitis, atopic keratoconjunctivitis, and vernal keratoconjunctivitis. Diagnosis seeks to identify the etiologic agent, and confirmation is given by conjunctival provocation testing. Treatment is based on avoiding contact with triggers, lubrication, topical antihistamines, mast cell stabilizers, immunosuppressants, and specific immunotherapy with the aim of achieving control and preventing disease complications.

Keywords: Ocular allergy, allergic conjunctivitis, rhinoconjunctivitis.

RESUMO

A alergia ocular, também conhecida como conjuntivite alérgica (CA), é uma reação de hipersensibilidade mediada por imunoglobulina E (IgE) do olho desencadeada por aeroalérgenos, principalmente ácaros da poeira doméstica e pólen de gramíneas. Os sintomas geralmente consistem em prurido ocular ou periocular, lacrimejamento e olhos vermelhos que podem estar presentes durante todo o ano ou sazonalmente. A alergia ocular tem frequência elevada, é subdiagnosticada e pode ser debilitante para o paciente. É potencialmente danosa para a visão, nos casos em que ocasiona cicatrização corneana grave, e na maioria dos pacientes associa-se a outros quadros alérgicos, principalmente rinite, asma e dermatite atópica. É classificada em conjuntivite alérgica perene, conjuntivite alérgica sazonal, ceratoconjuntivite atópica e ceratoconjuntivite vernal. O diagnóstico procura evidenciar o agente etiológico e a confirmação se dá pela realização do teste de provocação conjuntival. O tratamento baseia-se em evitar o contato com os desencadeantes, lubrificação, anti-histamínicos tópicos, estabilizadores de mastócitos, imunossupressores e imunoterapia específica com o objetivo de obter o controle e prevenir as complicações da doença.

Descritores: Alergia ocular, conjuntivite alérgica, rinoconjuntivite.

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Introduction

Ocular allergy, also known as allergic conjunctivitis (AC) is an immunoglobulin E (IgE)-mediated hypersensitivity reaction of the eye triggered by airborne allergens, primarily house dust mites and grass pollen. Symptoms usually consist of ocular or periocular itching, tearing, and red eyes, which may be present year-round or seasonally.[1]

Ocular allergy is highly frequent, underdiagnosed, and can be debilitating for the patient, and often challenging. It is potentially harmful to vision in cases where it causes severe corneal scarring, and in most patients it is associated with other allergic conditions, especially rhinitis, asthma and atopic dermatitis[1].

Eye anatomy

The eye in general can be divided into three parts: the outer layer (composed of the cornea and sclera), the middle layer (uveal-iris tract, ciliary body and choroid), and the inner layer, composed of the retina.

Conjunctiva

The conjunctiva is a thin, transparent mucous membrane that covers the sclera and also the eyelids, internally (a region known as the cul-de-sac).

It has rich vascularization, composed of connective and lymphoid tissue. Between the episclera and the conjunctiva there is Tenon's capsule, a thick collagenous membrane that surrounds the eye from the optic nerve to the limbus (Figure 1).

The first layer is the epithelial. Composed of goblet cells, single-celled glands that secrete mucin.

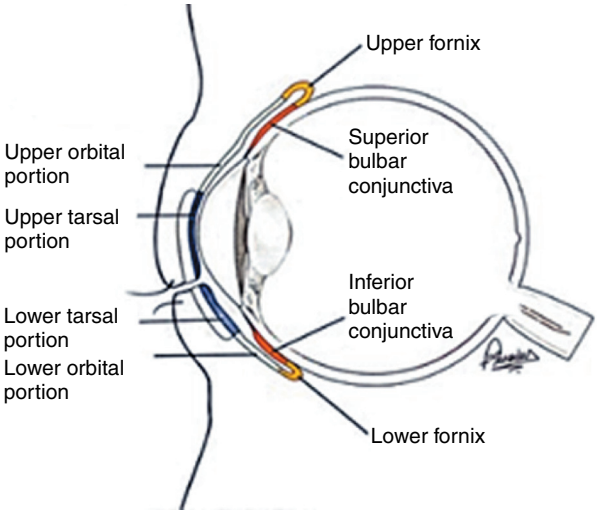


Figure 1
Anatomical aspect of the conjunctiva

Goblet cells can produce up to 2.2 mL of mucus per day. Mucus is essential for the integrity of the ocular surface as it lubricates and protects the epithelial cells. Mucin reduces the surface tension of the tear film to ensure its stability. Melanocytes: Melanocytes are mainly seen in the limbus, fornix, plica semilunaris, caruncle, and at the perforation sites of the anterior ciliary vessels. Sometimes they give the conjunctiva a brownish tinge. Langerhans cells: Langerhans cells are actually dendritic cells. Its main function is to process the antigen material and present it on the surface to other cells of the immune system. So, they function as antigen-presenting cells. The highest density of Langerhans cells was found in the tarsal conjunctiva, followed by the fornix and bulbar conjunctiva. The number of cells decreases with age.

The second layer is the substance itself. It consists of a superficial lymphoid layer and a deeper fibrous layer. It is rich in mast cells, lymphocytes, plasma cells and neutrophils.

Lymphocytes, mainly T lymphocytes, are found in abundance in the conjunctiva. They are present in the substantia propria and in the epithelium in a ratio of 2:3. Lymphoid aggregations similar to the mucosa-associated lymphoid tissue (MALT) found in the intestine and bronchi are also seen in the conjunctiva. These lymphoid aggregations consisting of T and B lymphocytes are known as conjunctival-associated lymphoid tissue (CALT).

Mast cells are basophils similar to granulocytic cells. The conjunctiva contains a large number of mast cells in the substantia propria. The total number of mast cells in the conjunctiva and adnexal tissue is approximately 50 million. Allergic conjunctivitis is a typical mast cell-mediated hypersensitivity reaction. In patients with allergic conjunctivitis, mast cells were also found in the conjunctival epithelium.

The third layer is fibrous, contains vessels, nerves and Krause's glands.

The function of the conjunctiva is to protect the ocular surface from external agents and maintain ocular lubrication, as the mucus produced by the conjunctiva helps to prevent eye dryness. It is divided into palpebral, bulbar and fornitial conjunctiva.

The palpebral conjunctiva is further subdivided into marginal conjunctiva, tarsal and orbital conjunctiva. The marginal conjunctiva is a transition zone between the eyelid skin and the conjunctiva proper. It begins in the intermarginal bands of the eyelid as a continuation of the skin. It consists of stratified epithelium. The marginal conjunctiva continues on the posterior surface of the eyelid for a short distance of 2 mm, to a shallow crease or crease, where it fuses with the conjunctiva proper. This sulcus is called the subtarsal sulcus.

The fornicial part is a fold that lines the cul-de-sac formed by the conjunctiva that covers the posterior surface of the eyelids to the conjunctiva that covers the anterior surface of the globe, this portion is thicker and weakly fixed to allow movement of the globe. It is divided into four regions, as described below.

The superior fornix lies between the upper eyelid and the globe. It extends 8 to 10 mm from the upper edge of the limbus. The inferior fornix lies between the lower eyelid and the globe. It extends to a distance of 8 mm below the bottom of the limbus. The lateral fornix is situated between the lateral corner of the eye and the globe. It extends a distance of 15 mm from the side of the limbus. The medial fornix is the shallowest and contains the caruncle and the plica semilunaris.

The bulbar conjunctiva is the thinnest of all parts of the conjunctiva, and so transparent that the sclera and underlying white vessels are clearly seen. It is loosely attached, except for a 3 mm zone near the limbus and near the insertions of the rectus muscles. The limbic conjunctiva is the part of the bulbar conjunctiva that covers the limbic region and fuses with the corneal epithelium.

Semiology of allergic conjunctivitis

Faced with a patient with suspected allergic conjunctivitis, we must establish the etiological origin of their condition and establish whether their symptoms are due to a primary condition or are secondary to other diseases, such as dry eye or blepharitis, which are frequent causes of conjunctival inflammation and whose treatment should focus on treating the underlying causes.[2]

For this, it is important to value the tools of the medical clinic, which include a good anamnesis, clinical exploration and the performance of complementary exams that allow us to establish an accurate diagnosis, and thus treat the patient correctly. The initial evaluation should include relevant aspects of the general eye examination and then focus on the specific examination of the allergic condition.

Anamnesis

You need to ask about the topics listed below.

- Duration of symptoms, their evolution and recurrence.
- Factors that exacerbate them.
- Single or two-sided presentation.
- Type of secretion: serous, mucous, purulent, filamentous, etc.
- Exposure to different environments and/or substances.
- Rubs ("friction") the eyes.
- Contact lenses: regimen use, lens type, hygiene, cleaning fluids, etc.
- History of allergies, asthma, eczema, atopy, etc.
- Topical and/or systemic drugs in use.
- Immune compromise: immunosuppression, chemotherapy, transplants, etc.
- Systemic diseases: atopy, Stevens Johnson syndrome, cancer, etc.
- Exposure to tobacco smoke: active or passive smoker, use of illegal drugs.
- Occupations and hobbies, exposure to air pollutants, travel, exercise habits, diet, etc.

Physical exam

The initial physical examination of the patient with allergic conjunctivitis includes assessment of visual acuity, external examination, and examination with a slit lamp.

It should include a detailed exploration of:

- regional lymphadenopathy: especially pre-auricular, in order to rule out infectious disease;
- skin: looking for signs of rosacea, eczema, seborrhea, etc.;
- abnormalities of the eyelids and appendages: inflammation, discoloration, ulcerations, nodules, loss of eyelashes, etc.;
- symptoms and signs: hyperemia, presence of follicles and papillae, adherence of eyelids, itching, irritation, pain, photophobia, blurred vision, epiphora, etc.

In addition, through the use of the slit lamp (biomicroscope), attention should be paid to:

- eyelid edges: inflammation, hyperedema or hypopigmentation, changes in the meibomian glands, keratinization, etc.;
- conjunctiva: laterality of symptoms, type of conjunctival reaction (follicular, papillary), distribution (diffuse, local), etc.;
- eyelashes: loss, trichiasis, secretions, parasites (demodex, lice);
- lacrimal system: puncture and channels;
- tarsal conjunctiva and fornix: follicles, scars, foreign bodies, etc.;
- bulbar conjunctiva: follicles, edema, nodules, chemos, laxity, papillae, ulcers, foreign bodies, keratinization, etc.

Complementary diagnostic tests[3]

In vivo diagnostic stains of the ocular surface

There are different substances with staining properties that can be used to study the ocular surface and that are very useful for the diagnosis and monitoring of patients with allergic conjunctivitis. These are fluorescein, rose bengal and lysamine green.

Target crops

Biopsy/brushing/shaved conjunctival

Blood/tear tests

Conjunctival provocation

Other diagnostic methods

Pathophysiology of allergic conjunctivitis

Allergic eye diseases are caused by direct exposure of the ocular mucosa to environmental allergens, which are dissolved in the tear and penetrate the conjunctiva to attach to IgE antibodies bound to the surface of mast cells.

Since the conjunctiva is an area of mucosa similar to the nasal mucosa, the same allergens that trigger allergic rhinitis may be involved in the pathogenesis of allergic conjunctivitis. Common airborne antigens, such as dust, fungi, pollen, and grasses, can cause the symptoms of acute allergic conjunctivitis, such as itching, redness, burning, and tearing.

In sensitized individuals, Th2 cells release proinflammatory cytokines (IL-4, IL-5, IL-13) that stimulate IgE production by B cells.[4]

The reactions produced can be divided into an initial stage lasting 20 to 30 minutes, which is related to the specific activation of conjunctival mast cells that causes their degranulation, releasing histamine, proteoglycans, proteases (tryptase, chymases), as well as the formation of mediators. lipids (prostaglandins and leukotrienes), interleukin (IL4, IL5, IL6, IL8, IL13) and tumor necrosis factor alpha (TNF-α). This reaction follows a late phase originated by the stimulation of epithelial cells and fibroblasts with the release of proinflammatory cytokines and chemokines and characterized by infiltration of inflammatory cells (neutrophils, eosinophils, lymphocytes and macrophages), with consequent persistent conjunctival inflammation. Unlike other allergic diseases, there is little eosinophilic infiltration in acute forms, which increase as the pathology becomes chronic.

Since the discovery of two functionally different subpopulations of CD4+ T cells (TH1 and TH2) some 30 years ago, it has quickly become evident that TH2 cells play a crucial role in the development of allergic respiratory tract inflammation. It has commonly been assumed that a th2 immune response and type I hypersensitivity form the basis of allergic conjunctivitis. The main factors contributing to the severity of AC are believed to be the allergen load on the ocular surface and locally produced specific IgE. Furthermore, there is a very significant correlation between the presence of allergen-specific IgE in tears and ocular allergy symptoms. This continuous release of histamine, together with the increased allergic load, leads to an expanding population of mast cells residing in the conjunctival tissue, thus perpetuating the allergic response. There is a general correlation between the degree of cellular infiltration and the severity of the disease. In addition, cell infiltration products are known to promote conjunctival irritation. In addition, connective epithelial cells and fibroblasts generate the allergic response, producing cytokines and other factors that maintain local inflammation and lead to tissue remodeling.[5]

It was found that new subpopulations of helper T cells–Th17 cells that produce interleukin-17 (IL-17) – play an important role in the pathogenesis of Th2-mediated conjunctivitis. Studies have shown that Th17 cells are involved in a variety of immune inflammation, including psoriasis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and asthma. However, the role of Th17 and IL-17 in allergic conjunctivitis is still unclear[6].

Epidemiology

There is a lack of international data on the prevalence of ocular allergy. In the United States, ocular allergy (OA) is estimated to affect 15-20% of the general population.[7] Ocular symptoms are believed to occur in 30-70% of patients with allergic rhinitis (AR),[8] and are more commonly triggered by intra-household than extra-domiciliary allergens.[9]

In Sweden, the estimated prevalence of allergic conjunctivitis was 19%, in Turkey, the prevalence of allergic conjunctivitis (AC) in children aged between 6 and 14 years was 7%. In Pakistan, the prevalence of conjunctivitis in patients aged 5 to 19 years was 19%.[10]

The prevalence of ocular allergy symptoms in Brazilian adolescents in 3,120 schoolchildren was 15.5%, considering the criterion of more than three episodes of ocular itching in the last 12 months. In this study, the prevalence of AC was higher in females, with 17.4% compared to males, with 13.3%. Genetic, hormonal factors and use of cosmetics are being investigated as possible causes.[11] In other studies, all eye allergy symptoms surveyed were significantly more prevalent in female adolescents, including eye itching, tearing, sensitivity to light, and feeling of grit in the eyes. Girls had more eye symptoms but lower sensitization rates than boys.[1,8]

In most studies, the most frequently related symptoms are: tearing (74%), followed by photophobia (50%) and foreign body sensation (37%). In these, the prevalence of allergic conjunctivitis was 20%, affecting more females than males (56% versus 46%; $p = 0.01$).[10] More recent studies show a trend towards a change in the prevalence of AC symptoms in relation to sex, being more frequent in childhood in boys and, after puberty, in girls.[8,9]

Allergic conjunctivitis (AC) is often underdiagnosed in patients with rhinitis and asthma. The diagnosis of conjunctivitis was recorded by the attending physician in 16% of 1549 asthmatics (mean age 4.3 years), however, 618 (44%) had at least one eye symptom that suggested ocular allergy (OA).[12]

AC alone has been estimated to be 6-30% of the general population. Seasonal allergic conjunctivitis is the most frequent form; however, studies from tertiary referral centers for ophthalmology report that the chronic forms, such as vernal and atopic keratoconjunctivitis, are the most frequently seen by ophthalmologists. A survey of 304 ophthalmologists showed that most patients with allergic conjunctivitis suffer from a few

episodes of mild, intermittent conjunctivitis annually. However, 30% of patients experience frequent episodes with intense and persistent symptoms. Treatment is often inappropriate.[9]

A study carried out in a Brazilian ophthalmology center evaluated 207 patients, of which 38% were diagnosed with spring keratoconjunctivitis; 39% as atopic keratoconjunctivitis; 13% as perennial allergic conjunctivitis and in 10% of patients there was no definite diagnosis. The presence of extraocular allergy was higher in patients with atopic conjunctivitis (91%), and lower in patients with spring (32%). The most intense symptoms were itching and tearing in patients with keratoconjunctivitis and there was a positive correlation between the intensity of symptoms and clinical signs.[13]

Triggers of conjunctivitis

The most common forms of allergic conjunctivitis (AC) are related to the type of allergen to which the patient was exposed and previously sensitized, and include perennial (PAC) or seasonal (SAC) allergic conjunctivitis. The difference between the two is given by the periodicity or persistence of symptoms. PAC is usually caused by indoor allergens such as house dust mites, pet dander, cockroaches, mold spores, or others. CAE is usually caused by pollen and is described more frequently in temperate climates, which are characterized by having four well-differentiated seasons during the year and presenting rains in the winter months, a climate present in Anglo-Saxon America, where a higher prevalence of SAC is reported.

The presence of pollens and other seasonal allergens such as extra-domestic fungi (eg *Cladosporium*, *Aspergillus*) depends on geographic and meteorological factors; mainly on the temperature and relative humidity of the environment. Minor household allergens, such as those from cats, dogs, and rodents, tend to become volatile and remain airborne longer, giving them the ability to produce severe or bothersome symptoms.[4] In contrast, house dust mites or cockroach allergens, due to their larger size, can only remain suspended for a few minutes in the air. Many patients are sensitized to more than one allergen, that is, they are polysensitized and may experience permanent symptoms with seasonal exacerbations. Being polysensitized seems to be associated with the persistence and severity of allergic diseases.[14]

The role of IgE-mediated allergy was clearly demonstrated in SAC and PAC, and two phases of inflammation were characterized. The initial phase, mediated by IgE, begins a few seconds or minutes after exposure to the allergen and lasts for 20 to 30 minutes. The late phase, which begins a few hours later, is responsible for ongoing inflammation, with persistent symptoms and risk of damage. Conjunctival allergen provocation tests are reproducible and used to confirm the diagnosis of AC by seasonal and perennial allergens, both in research studies and in clinical practice.

Ocular allergy to pollen in Latin America

Ocular symptoms (OS) associated with SAC occur when pollen dissolves in the tear film and passes through the conjunctiva. Twenty percent of individuals with pollinosis submitted to nasal pollen challenge present OS, suggesting that the same can occur without the direct contact of the allergen in the conjunctiva.[15]

Pollinosis is common in regions where there is a harsh winter, with low temperatures, followed by an exuberant spring (temperate or sub-tropical climate). Thus, in Latin America, it is prevalent in countries such as Argentina, Chile, Uruguay and southern Brazil (PR, SC, RS). However, it can be considered, eventually, also in tropical regions where there are high altitudes compensating for low latitudes.

Most studies focus on rhinitis, and few have examined ocular symptoms as an independent entity. OS is often described as nasal allergy symptoms, using the expression “allergic rhinoconjunctivitis” or simply “allergic rhinitis” or they combine all eye symptoms as OS.[16] This naturally complicates studies on the epidemiology of SAC, not only in Latin America, but also in other parts of the world.[17,18]

In Brazil, grass pollination is found basically in the southern states (PR, SC, RS), where the subtropical climate predominates, with well-defined seasons, unlike the rest of the country, with a tropical climate. Grasses are the main agent associated with changes in the external environment in recent decades, due to the increase in population and natural vegetation being replaced by agricultural and pastoral activities. Here, *Lolium multiflorum* (ryegrass) with intense allergenic activity can be included, in addition to *Cynodon dactylon* and *Paspalum notatum*.

Retrospective study on SAC, involving 876 patients with pollinosis in the area of Caxias do Sul, RS, Brazil, where all were sensitized to mixed grass pollen antigens, SAC occurred in 86.2% of cases, being classified as severe in 24.8%, with "symptoms difficult to tolerate interfering with daily activities and sleep".[19]

In the city of Bahía Blanca (AR), air pollen began to be recorded in 1995. Over the following years, intermittent and continuous aerobiological studies were carried out in the cities of Buenos Aires, Bariloche, Córdoba, Neuquén (Valle del Rio Negro), Mar del Plata, Paraná, Santa Fe, Santa Rosa, Mendoza and, recently, in the city of Trelew. In the city of Bahía Blanca, as in Buenos Aires, the skin sensitivity through allergen tests corresponded to the aerobiological counts and the geographic-regional representation of the studied species. Currently, data collection from some cities follows, and new challenges and questions are opening to be revealed in future research.

Many of the studies carried out so far can be found summarized in the Alergopalinological Atlas of the Argentine Republic, published in 2019 by the Argentine Association of Allergy and Clinical Immunology.

The prevalence of different plant species is mentioned according to aerobiological studies. Allergic skin sensitivity to pollen, or serological sensitivity, is associated with allergic rhinoconjunctivitis and/or asthma.

The subdivision of *Gymnospermae* in terms of aerial pollen is represented by the order *Pinales*, which comprises the *Cupressaceae*, which are a family of conifers of the order *Cupressales* of great economic and landscape importance worldwide. These species are present in almost all cities in Argentina and stand out mainly in the Patagonian mountain range, being one of the most abundant pollen species in the city of Bariloche. *Nothofagus*, also known as "southern beeches", is a genus of several species of trees and shrubs native to the southern hemisphere of America and Australasia.

In general, *Cupressaceae* pollen sensitivity represents low sensitivity to skin tests; however, they become symptomatically important, as they are the first pollens to appear in abundance. The incipient appearance of these pollens causes patients to experience the first symptoms of the pollen season, which sometimes cause the priming effect, which is increased sensitivity to other species that flower later. In addition, in the *Cupressaceae* family, there are many species that maintain a pollination of several weeks. In the study, there is allergic sensitivity to *Nothofagus* proteins, which still needs to be determined.[20-23]

The order *Lamiales,* which includes several subfamilies, is represented by the *Oleaceae*, consisting of varieties of *Fraxinus spp.* (ash), with high air pollination, but low skin sensitivity. Here, *Olea europae* (olive tree) and several species of *Ligustrum* (privet) were found, which represent a large number of pollen grains and accompany the flowering of grasses such as that early in the beginning of summer. Privet and olive showed significant sensitization in allergic patients both regionally and globally. The olive tree is important in the Bahía Blanca region for its use at olive oil production and in urban afforestation. The same occurs in the city of Mendoza, predominantly for commercial purposes. High sensitization to olive tree pollen was demonstrated in the city of Bahía Blanca. In other cities, such as Rosario and Buenos Aires, privet represents a higher prevalence in skin sensitivity and air pollen.[24-27]

The order of *Proteales*, represented by *Platanus spp.*, is an abundant species in the cities of Buenos Aires and La Plata, mainly in urban linear trees. Despite having a moderate amount of grains in the air, they showed that pollen causes greater sensitivity in patients with allergic rhinoconjunctivitis in CABA and, in the city of London, is responsible for moderate to severe allergic symptoms. Its pollination period (on the order of two weeks) may be a factor that aggravates or induces a greater sensitization to other pollens, as it seems to give continuity to the flowering of ash and cypress trees.[28,29]

The order *Fagales*, within the family *Betulaceae*, representatives such as Castanea native (chestnut, *Quercus spp.* - oak) and *Alnus spp.* (alder), have pollination periods of less than one month, and in some cases, only two weeks. Therefore, none of them represent a persistent causative agent of rhinoconjunctivitis, however in polysensitized patients, due to cross-reactions, they may contribute to the exacerbation of allergic symptoms.[30]

Poaceae, or ragmines, are the most representative pollens in aerobiological studies in almost all cities in Argentina, as well as in the rest of the world, where they are shown to be the most common cause of seasonal allergies.[31]

It is considered to be the most common cause of rhinoconjunctivitis symptoms, especially in early

summer, caused by the *Pooideae* subfamily and then, in late summer, by the flowering of the *Chloridoideae* and *Panicoideae* subfamilies. The *Chloridoideae* subfamily is well represented by *Cynodon dactylon*, and also by *Distichils spicata* in the city of Bahía Blanca, which demonstrated cutaneous sensitivity in patients with allergic rhinoconjunctivitis. This last herb is a perennial herbaceous species, native to America, Canada, Chile and Argentina. The second family, *Panicoideae*, is represented by *Paspalum notatum* and *Sorghum halepense*, called "elatior" in modern taxonomic classification. The species of the last two subfamilies are called "subtropical", have different photosynthesis and phenological behavior, with flowering later than that of the *Pooideae*, which are called "temperate". Subtropical grasses have a significantly similar grade to temperate grasses. Recent studies of these subtropical species describe their own allergens that they do not share with the *Pooideae*.[32,33]

There is a wide variety of species that do not belong to trees and grasses, which is often called a "weed group", or weeds, in English. This is a group that encompasses a large number of genera, making it difficult to use a single taxonomic name. In this group are the *Asteraceae*, the Angiosperm family with the greatest richness and biological diversity. In the Republic of Argentina, are prevalent, especially in regions pampeana and patagonia, on the east coast of the continent: *Salsola kali*, *Kochia scoparia*, *Chenopodium spp.*, and others stand out among them.

In other Latin American countries, several researchers can be listed who show results in aerobiological counts and in studies of skin sensitization to pollens. In Chile, Pedro Mardones demonstrated, in several studies, the prevalence of trees and grasses. In Uruguay, there are several multidisciplinary works on allergenic flora and air pollen in the cities of Montevideo and Concepción del Uruguay.[34] In Mexico, there is the Center for Aerobiological Studies that has several centers where they monitor the pollen in the air of different species. It should be mentioned that this Latin American country is located in the northern hemisphere.

Countries like Colombia, along with Venezuela and Ecuador, are located in Ecuador proper, and have a great plant diversity as a heritage, which is under study.

In Paraguay, for three years, in the city of Asunción, a group of allergists formed by Perla Alcaráz, Cinthia Perez, Rosmary Stanley and Pedro Piraino, has studied air pollen and presented important data such as the moderate presence of pollen grains along the year. The pollen of the species *Cecropia adenopus* stands out especially, which was previously classified as a tree of the *Moraceae*, but is currently in the family *Urticaceae*. Also called ambay, it is a tree belonging to the botanical family of *Cecropiaceae*. It grows in the marginal forests of the rivers of Brazil, in the Amazon region of Bolivia and Paraguay and in the northeast of Argentina. It can measure up to 15 meters in height, and its trunk has a diameter between 20 and 30 centimeters. The pollen of this species is the most prevalent in quantity and frequency, with an almost annual persistence. To date, there are no serological or skin sensitivity studies.

In Peru, Oscar Calderón has found pollen in several cities for over a year, the results of which will be published soon. Similarly, in Bolivia, Fabiola Ramallo recently started to monitor pollens from Santa Cruz de la Sierra. In a short time, these publications should be complemented with studies of allergic sensitivity to the pollens found.

Climate change, pollution and conjunctivitis

The ocular conjunctivae are richly vascularized and are constantly exposed to external factors. They are vulnerable to the adverse influence of bacteria, viruses, allergens, chemicals, and air pollutants, which can cause their inflammation.[35] Air pollution is one of the most important risk factors affecting people around the world,[36] especially the most vulnerable: children and the elderly.[37]

The eyes are vulnerable to air pollution, either by acute, short-term, or chronic exposure.[38] individuals who live in areas with a high level of pollution experience symptoms of conjunctivitis more often. Human eyes are only protected by a thin layer of tear film, and innervations present on the ocular surface are very sensitive to environmental chemicals.[39,40]

Air pollutants include: particulate matter (PM10, PM2.5), diesel exhaust particles (DEPs), gases (NOx, SO_2, O_3, CO and oxidants) in addition to organic compounds and metallic particles.[8] In large cities, the main source of pollutants is related to motor vehicle traffic, and the resulting pollutants (TRAPs) are a mixture of combustion-derived PM, DEPs and gaseous emissions, NOx, CO, oxidants and organic aerosols.[41]

The increase in exposure to high concentrations (> 10 μg/m^3) of CO, NO_2, SO_2, O_3 or PM, whether in the days before or on the day of emergency room care, has been accompanied by a significant increase in visits for conjunctivitis, as well as symptoms.[42-47] In addition, hot weather and strong winds, combined with the spread of pollen allergens, can potentiate these effects leading to ocular surface instability.[48]

Generally, the most severe forms of conjunctivitis are associated with greater damage related to environmental pollution.[41] Recent meta-analysis confirms air pollution as an important factorrisk for conjunctivitis. NO_2 followed by O_3 were related to the greatest impact, especially among women under 18 years old.[49]

Weather factors (humidity, temperature) can also affect eye health. Exposure to a controlled environment with low humidity has documented adverse effects on the evaporation rate, lipid layer thickness, stability and tear production on the tear film, generating significant ocular discomfort.[50] On the other hand, increased temperature may not directly induce eye discomfort like low humidity, but may lead to exacerbation of allergic conjunctivitis by raising pollen levels.[51]

Relationship between conjunctivitis and pollution: mechanisms

To date, the underlying pathophysiological mechanisms of conjunctivitis caused by air pollutants are still unclear. As human eyes are directly exposed to air pollution, some studies speculate that PM2.5[46,52,53] and PM10[54] particles could easily cause intraocular epidermal cells to become unadaptable, leading to cell death and inflammation tissue.[49]

Second, NO_2 and O_3 have strong oxidative stress effects, which can stimulate conjunctival cell inflammation[49]. NO_2 is an acidic gas, which upon entering the eye, easily changes the environment of the inner cells of the ocular epidermis, disrupts the function of eye cells, and causes inflammation.[55,56] It is plausible that the association between air pollution and the risk of conjunctivitis events is due to these potential mechanisms.[49]

Chronic exposure to air pollutants favors cellular damage, such as hyperplasia of the goblet cells of the epithelium on the ocular surface.[57] Exposure to DEPs increases the expression of cytokines, chemokines and growth factors in conjunctival epithelial cells, which means activation of conjunctival inflammation.[39]

All of these pollutants can directly damage the ocular surface by reducing the pH of the tear fluid or by oxidizing it. In addition, PM10 can cause dysregulated T cell responses and inflammation,[41] and is significantly associated with reduced Treg cell counts, as demonstrated in a birth cohort stud.[58]

Diseases associated with air pollution

Conditions associated with air pollution are mainly: eye irritation, discomfort, conjunctivitis, red eye syndrome and meibomian gland dysfunction.

Dry eye syndrome

Dry eye syndrome (SOS) is the most common eye condition[59] and has a frequency of 11% to 58%. Many factors can influence the occurrence of SOS symptoms: smoking, alcohol consumption, low humidity, air pollution, exposure to sunlight, sociodemographic factors, past eye surgery anduse of contact lenses (in this group the influence of air pollution is more noticeable).[60]

Among individuals living in large cities, tear film disorders occur more frequently.[61] A study carried out in Brazil showed an association between exposure to high concentration of NO_2 andtear film disorders, in addition to a sensation of ocular discomfort.[40]

Meibomian gland dysfunction

Meibomian glands are sebaceous glands, whose excretion is the outermost component of the tear film and prevents tears from evaporating from the surface of the eye. The symptoms reported by patients with Meibomian Gland Dysfunction (MGD) are: eye itching, feeling of discomfort, feeling of dry eyes and redness of the eyes. GMD is one of the most common causes of SOS.

Many factors influence gland function disorders, among others: chronic blepharitis, contact lens wear, Sjögren's syndrome, acne rosacea, humidity and air quality,[57] particularly high concentrations of NO_2.[40]

Blepharitis

Blepharitis is an inflammatory condition that covers the edges and skin of the eyelids, tarsal glands, and hair follicles eyelashes. The cause of blepharitis is mechanical (eg by dust, smoke), and also by bacterial infection. The connection between blepharitis and air

pollution is not well examined. A study carried out in Brazil showed a significant correlation between exposure to high concentrations of PM10 and CO in the air and an increased incidence of blepharitis on the day of exposure.[62]

Influence on the cornea

The cornea is constantly exposed to external factors such as atmospheric pollutants, ultraviolet radiation and cigarette smoke. Oxidative stress, which is an effect of these factors, favors corneal damage and visual impairment. PM2.5 concentrations between 20 µg/mL and 200 µg/mL are genotoxic, stimulate DNA damage and decrease the efficiency of corneal epithelial cells.[52]

Cataract

The frequency of cataracts is higher in developing countries, and the factors that help their formation are: age, sex, active smoking, exposure to ultraviolet radiation and diabetes. Individuals exposed to domestic burning of biomass (coal, wood, animal feces), especially for cooking, had a higher frequency of cataracts, especially among women[63]. In the case of using stoves powered by liquefied petroleum gas or biogas, the risk of cataracts was much lower. Lack of ventilation in the kitchen was an independent risk factor for cataract.[64]

Influence on retinal microcirculation

Air pollution has been identified as an independent risk factor for the development and progression of cardiovascular disease, however its influence on microcirculation is still poorly studied. Compared to changes in coronary macro and microcirculation, pathological lesions in the retinal vessels are justified, indicative of atherosclerosis.

A Brazilian study evaluated the association between air pollution and retinal vessel narrowing and demonstrated a narrowing of the central retinal arteriolar equivalent (CRAE) of 0.8 µm in response to chronic exposure (2 years) to PM2.5 (3 µg/ m^3) in more than 4,500 individuals.[65] At acute exposure, on the day before the evaluation, the highest concentration of PM2.5 (7 µg/m^3) determined a narrowing of the CRAE by 0.4 µm. Louwies et al.[66] measured retinal vessel diameter in 85 healthy subjects and assessed how short-term exposure to PM10 and carbon dust affects them. CRAE narrowing by 0.93 µm and central retinal venular equivalent (CRVE) narrowing by 0.86 µm was observed with every 10 µg/m^3 increase in PM10 concentration.

These findings draw attention to the fact that not only chronic but also short-term exposure to air pollutants causes abnormalities in the retinal microcirculation, which can cause disturbances in retinal nutrition and oxygenation, which can lead to visual impairment. Retinal microcirculation disorders may also impact cardiovascular incidents in the future.[38]

Comorbidities

AC can have a significant impact on quality of life, affecting sleep and causing emotional problems and impairment of activities of daily or social living, such as productivity at work or school performance. AC occurs concurrently with allergic rhinitis (AR) and other allergic diseases in most patients, at least 60% of patients with allergic conjunctivitis may have rhinitis.[67] Ocular symptoms may also be present without nasal involvement in 2 to 7% of patients with AC.[68,69] Asthma and atopic dermatitis are other common comorbidities. In adolescents, most epidemiological data, including data from different phases of the International Study of Asthma and Allergies in Childhood (ISAAC), associate ocular and nasal symptoms, making it difficult to separate the prevalence of AC from allergic rhinitis.

A study carried out in Shanghai analyzed the prevalence of symptoms of ocular allergy, allergic rhinitis, asthma, atopic dermatitis and sensitization to dust mites, pollen and food in a population of children and adolescents. The overall prevalence of symptoms of AR, diagnosed asthma, and diagnosed atopic dermatitis was 40.4%, 11.6%, and 16.7%, respectively. Young children had a higher prevalence of being diagnosed with allergic rhinitis and atopic dermatitis than adolescents. There were gender-associated differences in the prevalence of allergic rhinitis and asthma among young children, but not among adolescents. Sensitization to mites, food, and pollen was associated with a higher prevalence of allergic diseases.[70]

A survey conducted by the American College of Allergy, Asthma and Immunology found that 35% of families surveyed had allergies, of which more than 50% reported associated eye symptoms.[71] The importance of AC is mainly due to its frequency, which varies from 5% to 22% of the population.[72]

A study carried out by Geraldini M. et al., which included 3,120 patients between 12 and 18 years of age, found a prevalence of symptoms of allergic conjunctivitis of 20.7%. At least one comorbidity (asthma, rhinitis, or atopic eczema) was reported by 75.3% of children with AC. Rhinitis was the most frequent comorbidity (64.6%). Asthma appeared in 31.4%, and atopic eczema in 13.1%. The percentage of children with none, one, two or three comorbidities related to allergic conjunctivitis was 24.7%, 44.7%, 27% and 3.6%, respectively. Those patients with perennial symptoms were more frequently associated with the three comorbidities compared with those with seasonal symptoms (66.7% versus 56.9%; p = 0, 034), while asthma and topical eczema did not differ between the two groups (33.1% versus 24.8%; p = 0.062) and (12.3% versus 16%; p = 0.25), respectively. The probability of an adolescent with AC having asthma, rhinitis and atopic eczema was (OR = 5.7; 95% CI: 4.5 to 7.1); (OR = 3.6, 95% CI 3.0 to 4.3) and (OR = 2.6, 95% CI 2.0 to 3.5), respectively. The association between asthma and AC was greater among those with AC and rhinitis than among those with AC alone (36.8% versus 20.5%; p < 0.01).[1]

Classification of allergic conjunctivitis

To date, several methods and nomenclatures have been proposed to classify the different forms of ocular hypersensitivity, the most accepted and used classification being adopted by the European Academy of Allergy and Clinical Immunology (EAACI),[73] which encompasses two groups: hypersensitivity non-allergic ocular and ocular allergy, which in turn is subdivided into IgE-mediated forms – such as seasonal (SAC) and perennial (PAC) allergic conjunctivitis and more than half of the cases of vernal (VKC) and atopic (AKC) keratoconjunctivitis) – and non-IgE-mediated forms, which include some cases of the latter two forms, as well as contact blepharoconjunctivitis (CBC) (Figure 2).

The different ocular hypersensitivity disorders range from mild situations, usually intermittent and with acute symptoms (SAC, PAC and CBC) to moderate to severe forms, usually chronic and that can affect vision (giganto-papillary conjunctivitis, VKC and AKC).

The main differentiating characteristics of the different ocular hypersensitivity disorders are summarized in Table 1.

Allergic conjunctivitis

Allergic conjunctivitis is the most frequent form of ocular allergy and involves IgE-mediated mechanisms, causing bilateral ocular symptoms that are usually associated with the presence of rhinitis. The most characteristic symptom is ocular pruritus, and tearing, conjunctival hyperemia, eyelid edema and mild papillary hypertrophy of the tarsal conjunctiva may also occur.[73] Corneal involvement is rare, but blurred vision may occur.[8]

Depending on the frequency of symptoms, it is subdivided into seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC).

In SAC, symptoms are intermittent and more prevalent in spring and autumn, when pollen levels are highest. In PAC, symptoms are persistent and arise related to exposure and sensitization to perannual allergens, such as dust mites, dust mites and fungi, or due to the presence of multiple sensitizations.

Vernal keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is a rare, persistent and severe form of ocular allergy, which occurs mainly in areas with a warm climate, such as the Mediterranean basin, North Africa and the Middle East. It is typically seasonal (spring to late summer) and most commonly affects male children (male/female sex ratio 3/1), aged 4-12 years, disappearing after puberty. Approximately 50% of patients have no history of atopic disease or allergic sensitization, which suggests that VKC is not a fully IgE-mediated pathology.[8]

The first symptom to appear is intense bilateral eye itching, usually triggered by non-specific stimuli such as wind, dust, strong light or physical exertion, followed by extreme photophobia, burning and foreign body sensation and, often, blurred vision. Conjunctival injection, ptosis, mucous and creamy secretion and blepharospasm are observed.

There are three major forms of the disease: tarsal, limbic and mixed. In western countries, the tarsal form is the most frequent, while in subtropical countries the limbic form, also known as tropical endemic limboconjunctivitis, predominates. The tarsal form is characterized by the presence of giant papillae (between 7 and 8 mm in diameter) in the upper tarsal conjunctiva that resemble cobblestones, infiltrated by fibrin and mucus (pseudomembrane). In the limbic form, there are limbic papillae with white outgrowths

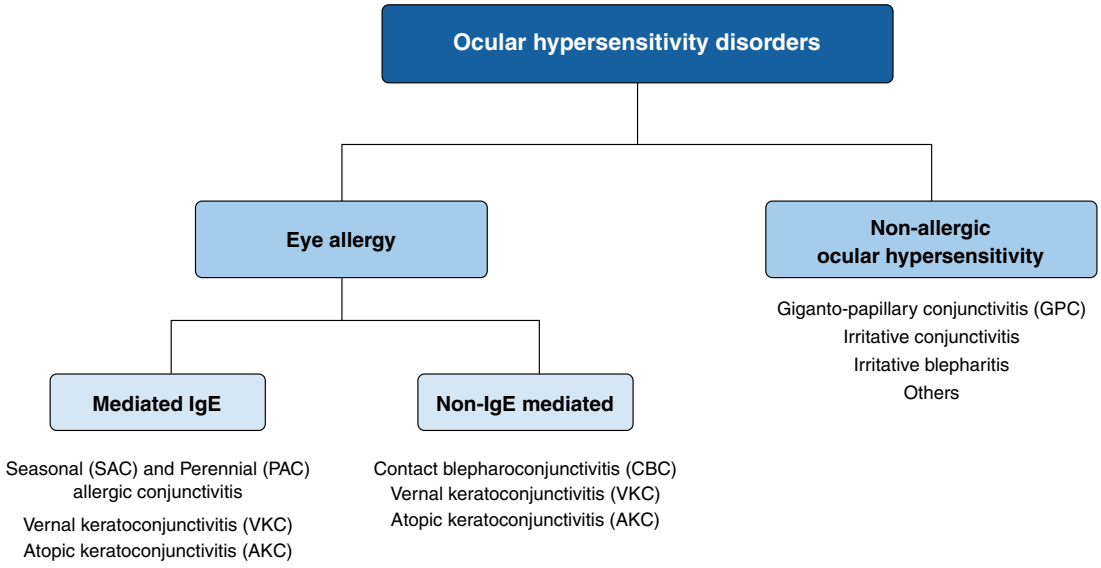


Figure 2
Classification of ocular hypersensitivity disorders
Adapted from Leonardi A et al.[73]

at the apexes, with a gelatinous appearance – Horner-Trantas nodules. Corneal involvement arises: punctiform keratopathy or round "escutcheon" ulcer, and there is a high incidence of keratoconus in these patients, and the most severe cases can lead to blindness.

Atopic keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is a chronic inflammatory ocular pathology, with bilateral involvement in the eyelids, conjunctiva and possibly the cornea. It corresponds to the entity with the highest risk of blindness and occurs in adults (18-50 years) who have systemic manifestations of atopy, namely atopic dermatitis. Its prevalence in patients with atopic dermatitis varies between 20% and 77%, and corresponds to one of the most serious ophthalmological complications of atopic dermatitis. There is usually a family history of other atopic diseases with elevated serum IgE levels. In its pathogenesis, IgE, Th2 and Th1 mediated mechanisms are involved. Unlike VKC, which rarely goes beyond 5-10 years of evolution, AKC can last for decades.

Clinically, it is similar to vernal conjunctivitis, with formation of (minor) papillae on the upper tarsus. A characteristic sign is eyelid eczema which tends to harden and crack, the eyelids are often inflamed, macerated and crusted – chronic blepharitis. It may be associated with eyelid colonization by *Staphylococcus aureus* and meibomian gland dysfunction. The development of keratopathy with neovascularization is particularly severe and is relatively frequently complicated by cataracts, herpes simplex, keratoconus, chronic blepharitis, conjunctival fibrosis, and retinal detachment, with sustained deterioration of vision.

Contact blepharoconjunctivitis

Contact blepharoconjunctivitis (CBC) is a form of non-IgE-mediated ocular allergy in which contact dermatitis occurs on the eyelids, with or without extraocular dermatitis and with possible involvement of the conjunctiva. It often affects middle-aged or older women.[9]

It arises associated with the repeated use of eye medication "drug conjunctivitis", due to toxicity or contact sensitization to the constituents of the drugs, usually preservatives. In addition to the constituents and preservatives of eye topicals, also various cosmetic products and metals may be involved as causal agents. Cosmetics applied to the hair, face or nails can be inadvertently transferred to the eyes, causing sensitization, sometimes without any symptoms at the point of origin, where the epidermis is thickest.

The most frequent symptoms are itching and burning sensation in the eyelids, with detection on physical examination of edema, erythema, eczema or lichenification of the eyelid skin, conjunctival hyperemia and papillae.

Table 1
Characteristics of main ocular hypersensitivity disorders

	SAC	PAC	VKC	AKC	CBC	GPC
Incidence	++++	++	+	+/–	–	–
Presentation	Intermittent	Persistent	Persistent with exacerbations flashing	Chronic	Chronic with exacerbations flashing	Persistent
Mechanism immunological	IgE	IgE	IgE/Non-IgE	IgE/Non-IgE	No IgE	Not allergic
Clinical context	Rhinitis allergic	Rhinitis allergic	Atopy	Dermatitis atopic	+- dermatitis contact at other places	No atopy
Age/Sex	Start childhood/ young adult	Start childhood/ young adult	++ Children sex M (M/F = 3/1); resolution > 20	++ Adults (18-50 years old)	++ Women middle-aged or older (F/M = 2/1)	–
Eyelids	Edema	Edema	Edema, ptosis	Eczema, blepharitis	Eczema	–
Conjunctivitis	Papillae	Papillae	Papillae giants	Papillae giants	Hyperemia	Papillae giants
Cornea	–	–	Nodules of Horner-Trantas, ulcers, CPS	Nodules of Horner-Trantas, ulcers, CPS	–	Rare

SAC = seasonal allergic conjunctivitis, PAC = perennial allergic conjunctivitis, VKC = vernal keratoconjunctivitis, AKC = atopic keratoconjunctivitis, CBC = contact blepharoconjunctivitis, GPC = giganto-papillary conjunctivitis, CPS = superficial punctate keratitis.

Non-allergic ocular hypersensitivity

Non-allergic ocular hypersensitivity includes several entities, namely giganto-papillary conjunctivitis (GPC), irritative conjunctivitis, irritative blepharitis, among others.

Giant papillary conjunctivitis

Giant papillary conjunctivitis (GPC) arises in the context of non-allergic hypersensitivity to products that chronically contact the ocular surface, most often contact lenses and their cleaning products and preservatives, ocular prostheses or postoperative sutures. The mechanism involved is related to chronic mechanical trauma.

Clinically, it resembles other forms of ocular hypersensitivity, and may cause symptoms of eye itching, foreign body sensation, blurred vision and production of mucous secretions. Sometimes there is a worsening of symptoms in the spring season. The patient develops a papillary reaction in the upper eyelid (with or without keratopathy), which is more common with soft contact lens wear (5-10%) compared with hard contact lenses (4%).

Usually, GPC resolves when contact lens wear is discontinued or when the foreign body that is in contact with the ocular surface is removed.

Diagnosis of allergic conjunctivitis

Serological and skin tests in the assessment of ocular allergy

The diagnosis of different conjunctivitis is clinical. The etiology is determined by screening for aeroallergen-specific IgE. In vivo test, allergic skin prick test, must be performed by a trained professional, being easy to perform, low cost, high sensitivity and specificity. Specific IgE is identified for mites, pollens, animal epithelia, cockroaches and fungi. In vitro serum specific IgE testing can also be used to identify allergy to the same aeroallergens as the skin test. More recently, single or multiple IgE detection platforms have been developed for specific proteins from allergen sources, called components, and this has brought us closer to Precision Medicine. There is a need for a specialized laboratory, higher cost, but also with good sensitivity and specificit.[74]

Skin prick tests are still the main tool for diagnosing the allergic phenotype of airway disease in the allergist's daily practice. Total serum IgE, in turn, seems to be correlated with the complexity of the IgE repertoire,[75] and specific serum IgE is very useful in the pediatric population and as an adjunct or replacement to skin tests.[76]

However, the vast majority of commercially available diagnostic tests and vaccine extracts use solid phase allergens obtained from the original source through protein extraction and purification. The availability of a broad panel of recombinant or highly purified allergenic molecules for in vitro diagnosis has profoundly changed the basic knowledge in the area, but also the conduct in clinical practice.[77] Furthermore, it is now possible to define the patient's IgE repertoire using these species-specific and cross-reactive allergenic molecules.[78] This has become a brilliant solution, particularly in so-called “polysensitized” patients, and not only in food allergy or hymenoptera, but also in respiratory allergy.[76] Until the present moment, There are few data in the literature regarding the use of component resolved diagnosis (CRD), particularly with the multiplex technology, in allergic diseases of the upper airways (AR and allergic conjunctivitis), especially with regard to the so-called “perennial allergens”, such as mites, fungi and animal epithelium. In this section, we will review the available publications on CRD in allergic rhinoconjunctivitis (RCA), particularly studies on the sensitization profile in these patients, what there is data divided by allergen sources, and some news on methods that can help in the management of more severe conjunctivitis. by detecting specific IgE in the tear. Especially with regard to so-called “perennial allergens”, such as mites, fungi and animal epithelia. In this section, we will review the available publications on CRD in allergic rhinoconjunctivitis (RCA), particularly studies on the sensitization profile in these patients, what there is data divided by allergen sources, and some news on methods that can help in the management of more severe conjunctivitis. by detecting specific IgE in the tear. Especially with regard to so-called “perennial allergens”, such as mites, fungi and animal epithelia. In this section, we will review the available publications on CRD in allergic rhinoconjunctivitis (RCA), particularly studies on the sensitization profile in these patients, what there is data divided by allergen sources, and some news on methods that can help in the management of more severe conjunctivitis. by detecting specific IgE in the tear.

Sensitization profile in patients with rhinoconjunctivitis

As we have already highlighted, the literature is scarce in relation to RCA, in particular with regard

to the sensitization profile of this population using this method. Two recently published series in Asian populations evaluated the multiplex component IgE detection technique in atopic patients and compared it with traditional skin tests or the FEIA method.[79,80]

In the Singapore study, atopics with RA, asthma and AD were evaluated and it was found that sensitization to mites was associated with the RA phenotype, while asthma and AD did not have a predominance of a single Ag. Furthermore, the ISAC did not prove to be useful as a screening tool if the major suspicion (clinical or epidemiological) was monosensitization.[80] In the survey carried out in Korea, it was shown that the agreement between ISAC and FEIA is quite high for *Dermatophagoides* mites, but the same was not true for birch pollens and the fungus *Alternaria alternata*, for which the sensitivity of FEIA was higher to ISAC.[79]

In a British cohort of live births, reassessed at the age of 11 years, the multiplex technique was used to assess patterns of sensitization and its relationship with atopic diseases presented by children. It was found that children with rhinoconjunctivitis were more sensitized to mites and pollens, while asthmatics were sensitized not only to these two sources of Ag, but also to animal epithelia. Finally, those with eczema were more sensitized to eggs and bovine Ag.[81]

A study in elite athletes participating in the Beijing Olympics evaluated 72 polysensitized individuals (defined based on skin test results) using the ImmunoCAP-ISAC method. The athletes were classified into four groups according to the clinical picture presented: allergic rhinoconjunctivitis, asthma, food allergy and asymptomatic. In addition to being useful in differentiating true polysensitized patients from those with positive cross-reactivity Ag tests, the method confirmed that the rhinoconjunctivitis phenotype was more associated with monosensitization, whereas asthmatics were more frequently polysensitized.[82]

In a retrospective study carried out in the western part of the Czech Republic, using the ImmunoCap-ISAC® multiplex platform for the detection of specific IgE, the results of 1,331 patients treated between December 2011 and June 2013 were analyzed. Results show that in 826 patients with a median age of 32.6 years old, the samples tested positive for at least one pollen-derived component, 62% of them were diagnosed with rhinitis. The highest level of sensitization was to grass components (81%), with Phl p 1 (69.6%) being the most frequent, followed by components derived from *Betulaceae* (54.8%), where Bet v 1 (54 .2%) was the most prevalent. Sensitization to components derived from *Cupressaceae* (14.1%), *Oleaceae* (10.8%) and Pla a 2 trees (15.5%), were less prevalent.[83]

In a study with 120 atopic patients with rhinoconjunctivitis and/or asthma, the microarray technique (ISAC CRD 103) was compared with FEIA (ImmunoCap) for the diagnosis of allergy to grass and cypress pollens. Both microarray and Cap showed high sensitivity (S) and specificity (E) in detecting grass allergy (ISAC: S = 97.7% and E = 92.3%; Cap: S = 95.3% and E = 96.1%) showing agreement between the two techniques. In the detection of allergy to cypress, ISAC showed similar sensitivity to Cap, but higher specificity (ISAC: S = 91.7% and E = 91.3%; Cap: S = 91.7% and E = 80.4%, p = 0.034).[84]

In South Korea, 168 adult patients with allergic rhinitis were evaluated and the detection of specific IgE by ImmunoCap and ImmunoCap-ISAC® for birch and mugwort pollens, among other aeroallergens, was compared. ImmunoCap sensitivity for birch was 86.9% versus 43.6% for ImmunoCap-ISAC®,κ = 0.511. In the case of mugwort, the sensitivity by ImmunoCap was 92.3% against 69.2% by ImmunoCap-ISAC®, κ = 0.670.[79]

In a study of 101 adults with rhinoconjunctivitis in Germany, the detection of specific IgE for 8 grass components (rPhl p 1, rPhl p 2, nPhl p 4, rPhl p 5b, rPhl p 5b, rPhl p 6, rPhl p 7, rPhl p 11 and nPhl p 4) single and multiplex platform, ImmunoCap and ImmunoCap-ISAC®. The correlation coefficient was significant in seven components [0.88 (rPhl p 1), 0.96 (rPhl p 2), 0.70 (nPhl p 4), 0.94 (rPhl p 5b), 0.92 (rPhl p 6), 0.85 (rPhl p 11), and 0.78 (rPhl p 12)], the exception being rPhl p 7.[85]

In Curitiba, 101 children with allergic rhinitis underwent skin test for *Lolium multiflorum* pollen, among other aeroallergens, and specific IgE measurement by multiplex platform ImmunoCap ISAC version 103. Allergic sensitization to *Lolium multiflorum* pollen determined by allergic skin test was 14.9%, whereas the most frequent sensitization to grass components was Cyn d 1 in 16.8%, Phl p 1 and Phl p 4 in 14.8% and 12.9%, respectively.[86]

Clinical application of the components in conjunctivitis

As already mentioned, the use of the multiplex chip in the RCA in relation to sensitization to dust mites,

both *Dermatophagoides* and *Blomia tropicalis*, showed accuracy comparable to the FEIA and prick tests. In addition to these data, Der p 1 and Der p 2 components have been shown to correlate with atopy and anti-Der p IgE serum levels, unlike Der p 10 and MUXF3 (bromelain) components.[87,88] Another application of ImmunoCAP-ISAC in relation to mite sensitization was demonstrated in a French study published in 2012, in which it was shown that sublingual immunotherapy with extract of *Dermatophagoides pteronyssinus* + *farinae* for one year did not induce new sensitization to the three Der p allergens (1, 2 and 10).

Regarding sensitization to fungi, there are no studies particularly carried out in RCA using the multiplex microarray technique. A retrospective study in children with ACR or asthma compared the Alt a 1 component measured by the FEIA method and the *Alternaria* allergen source, and showed that the accuracy of both is quite comparable, allowing either to be used to diagnose this sensitization.[89]

As much as allergens from so-called "furry" animals are more associated with asthma, there are some published data regarding RCA and the use of the multiplex technique. The main fact to be known by the attending physician to the patient exposed or sensitized to domestic animals, particularly dogs and cats, is that albumins (examples Fel d 2, Can f 3) are proteins that do not cause symptoms and have cross-reactivity between si, whereas lipocalins (Can f 1 and Can f 2) and secretoglobins (Fel d 1) are associated with clinical reactivity and do not have molecular mimicry. In this context, it has been suggested that the ImmunoCAP-ISAC could be indicated with a view to differentiating sensitization from allergy, or even to assess individuals at greater risk for future reactivity according to the degree of exposure.[90] A recently published Swedish cohort study showed that the Fel d 1 and Can f 1 components documented by the multiplex chip were better predictors of allergy evolution over time than cat and dog extracts.[91]

The multiplex platform has been used to detect early sensitization to pollen components and subsequent development of allergic rhinitis. In a German birth cohort, followed up to 13 years of age, a questionnaire was applied and blood samples were collected from 820 children aged 1, 2, 3, 5, 6, 7, 10 and 13 years. Diagnosis of pollen-related seasonal allergic rhinitis was performed according to nasal symptoms. Specific IgE antibodies to *Phleum pratenses* and 8 components were performed by FEIA and multiplex platform. One hundred and seventy-seven developed seasonal allergic rhinitis. Sensitization to Phl p 1 was early and the most common (78%)[92] in children with allergic rhinitis. Sensitization at 3 years predicts allergic rhinitis at 12 years, PPV = 68% and PPV = 84%.[93] In another study in children that used a multiplex platform for the detection of specific IgE, the serum of 764 individuals was evaluated to investigate the pathogenesis of IgE positive for proteins of the PR-10 family and birch allergic rhinitis at 16 years of age. Questionnaire and serum were collected at 4, 8 and 16 years of age from children in Stockholm, and performed ImmunoCap-ISAC. The risk of persistent allergic rhinitis to Bet v 1 at age 16 years was eight times greater (OR = 8.2) when the child had PR-10 sensitization at age 4 years.

Detection of specific IgE in the tear

Two recent studies used the multiplex microarray technique to detect allergenic components in tears in patients with ocular allergy, one being a case report[94] and the other a series of 10 patients with vernal keratoconjunctivitis.[95] Both showed that component-specific IgE is quantifiable by the ISAC method in the tear and may differ from the serum-specific IgE results. These data suggest that, in the near future, CRDs in secretions may be incorporated and collaborate in the etiological diagnosis of allergic diseases, particularly those that are difficult to define, such as vernal keratoconjunctivitis, for example.

Conjunctival allergen provocation test

The conjunctival allergen provocation test (CAPT) is a diagnostic tool to investigate IgE-mediated external ocular surface hypersensitivity diseases by evaluating the inflammatory effects caused by the conjunctival application of the allergen in a previously sensitized individual.[96] The purpose of the test is to accurately reproduce the signs and symptoms (eye itching, conjunctival redness, tearing, chemosis, and conjunctival/eyelid swelling) of allergic conjunctivitis (AC). Allergen-specific conjunctival hyperreactivity (eHRC) triggered by CAPT is a cascade of inflammatory events typical of an IgE-mediated hypersensitivity, which affects the conjunctival mucosa of individuals previously sensitized to the tested allergen and genetically predisposed. Positive CAPT causes the same signs and symptoms of AC in the tested eye that occur during natural exposure to the allergen. By triggering HRCe, CAPT confirms the allergen tested as the etiologic factor of ocular allergy.[97]

Conjunctival provocations with pollen grains to diagnose pollinosis (hay fever) and measure patient tolerance during desensitization experiments with pollen extracts were performed by Blackey in 1873. Until the 1970s, CAPT was used mainly for diagnostic purposes, but currently it has also been used to study the pathophysiology of AC, to evaluate the efficacy of topical ocular medications and of allergen-specific immunotherapy.[98] Another indication of CAPT is as an alternative test to assess mucosal reactivity in other IgE-mediated allergic diseases such as rhinitis, asthma, food allergy, and latex allergy.[99]

Recently, a publication by the EAACI Ocular Allergy Interest Group gathered recommendations for the clinical practice of CAPT.[99]

When to perform

Most cases of ocular allergy are benign, IgE-mediated conjunctivitis, of intermittent (seasonal allergic conjunctivitis) or persistent (perennial allergic conjunctivitis) evolution, for which an allergic cause must always be sought. Identification of aeroallergens is generally performed by skin prick tests (TCA) or by serum IgE-specific to the total allergen (S-IgE) or its molecular components.[100]

TCA and serum allergen IgE levels show good correlation with CAPT. Abelson et al.[97] observed 84% of positive CAPT in 396 individuals with positive TCA and suggestive history of AC, suggesting the routine use of the allergic skin test as a diagnostic tool for ocular allergy. Reactivity to the same allergen that presented positive TCA was detected by CAPT in 94% of subjects with eye complaints, which demonstrates a high positive predictive value of TCA in predicting a positive conjunctival challenge to the allergen, when there is a suggestive clinical history.[101]

However, positive TCA and elevated S-IgE only indicate sensitization to a specific allergen. Leonardi et al.[102] found an agreement of 81% of positive results of TCA and S-IgE to the same allergen with positive CAPT. In cases where there was no agreement, there was greater positivity of skin tests and/or serological tests (23%) in relation to ocular provocations (6%). Thus, the use of skin and serological tests, without proof by ocular provocation, could lead to an increase in the number of false positive cases of AC. Importantly, systemic sensitization can occur without clinical allergy, and local symptoms can occur without evidence of systemic sensitization. In another study, a significant correlation of elevated tear levels of allergen-specific IgE occurred only with positive conjunctival provocation, and not with TCA and S-IgE. These findings suggest the possibility that the conjunctiva is the only sensitized target organ in allergic individuals.[103]

For diagnostic purposes, CAPT is the only method that confirms a specific conjunctival response to a suspected allergen based on the clinical history in cases of SAC and especially PAC.

CAPT is particularly indicated when sensitization is inconsistent with clinical history, when a patient is polysensitized, or when skin or serological tests are negative or contradictory despite a medical history strongly suggestive that a specific allergen is involved in the ocular pathology. For SAC and PAC, detection of the most relevant allergen is critical before initiating allergen-specific immunotherapy.[99]

In vernal keratoconjunctivitis (CCV), SCPT is not routine practice and is used to identify allergens for immunotherapy in drug-resistant cases.[104]

CAPT is also widely used to study the pathophysiology of different forms of ocular allergy, for cell collection, measurement of chemical mediators, cytokines and other inflammatory biomarkers.[105]

Another indication of CAPT is for the follow-up of allergen-specific immunotherapy and for the evaluation of the antiallergic effect of topical drugs for the treatment of AC, being a method recognized by the Food and Drug Administration (FDA) for these purposes.[106]

There are some studies of the use of CAPT to confirm some cases of occupational latex allergy and food allergy. In a population of 174 children with suspected food allergy to cow's milk, egg, peanuts, and fish, negative CAPT excluded clinical food allergy, regardless of the serum IgE value to the allergen. Likewise, positive CAPT confirmed IgE-mediated food allergy.[107]

Practical recommendations for carrying out the CAPT

Prior to conjunctival provocation, patients must be asymptomatic, without active conjunctivitis or rhinitis, and unstable asthma. CAPT should be avoided in individuals with a history of eye surgery and recent infectious and inflammatory ocular pathologies (< 6 months), pregnant and lactating women, immunodeficiencies, neoplasms, liver or kidney failure, autoimmune diseases, cardiovascular diseases

using beta-blockers or who may decompensate if adrenaline is needed to treat a possible anaphylactic reaction.[100]

A complete eye examination must be performed before the challenge to rule out any conjunctival inflammation, being essential in cases of chronic conjunctivitis, when the presence of an ophthalmologist during the ocular provocation, in addition to the allergist, is necessary. Examination of the conjunctiva for mild chemosis visible only to the slit lamp can prevent high doses of allergens from being used during challenge, and thus prevent the onset of a late-phase reaction that could cause severe exacerbation of chronic conjunctivitis.[99]

There is no recommendation for performing CAPT in ocular surface pathologies that are not caused by IgE-mediated hypersensitivity, such as keratoconjunctivitis sicca, blepharitis and blepharoconjunctivitis, giant papillary conjunctivitis due to intolerance to contact lenses or foreign body, contact blepharoconjunctivitis with suspected allergy to eye drops, medications and cosmetics preservatives.[96]

CAPT cannot be performed during the period of natural exposure to the allergen, such as during pollinosis.[97]

Oral and topical topical medications that may interfere with the outcome of the conjunctival reaction should be discontinued prior to CAPT. H1 antihistamines, mast cell stabilizers, and topical ocular corticosteroids should be discontinued for at least two days prior to challenge. For cyclosporine and topical nonsteroidal anti-inflammatory drugs, the withdrawal period is for at least one week. Oral antihistamines should be discontinued one week prior to CAPT (three weeks for ketotifen), oral corticosteroids for two weeks, and antileukotrienes for three weeks.

As with other types of in vivo provocation, the consent form informing the risks and benefits of CAPT must be provided, discussed and signed by patients or legal guardians prior to conjunctival provocation. CAPT can be performed on children and adults, but requires cooperation and understanding of the procedure for a reliable result.[96,99]

The place for performing the CAPT (offices and hospitals) must have a structure for the treatment of possible serious adverse effects, such as asthma exacerbation, acute urticaria and anaphylaxis. Rescue medication, such as H1 antihistamine and topical and systemic corticosteroids, short-acting bronchodilators, and adrenaline, should always be available. Any positive CAPT should be treated with a topical ocular H1 antihistamine, and the subject should remain at the test site for 2 hours or until symptoms have completely disappeared. Ocular corticosteroids and oral H1 antihistamine should be considered in severe reactions that may progress to a late-phase reaction. These individuals should be monitored by medical staff for 24 hours.[99]

A summary of CAPT indications and contraindications is provided in Table 2.

Performance

CAPT has high sensitivity and allergen specificity for the diagnosis of allergic conjunctivitis in the presence of suggestive symptoms, when performed with standardized allergen extracts.[101,108]

Extract quality is critical for reliable results. Extracts must be standardized, preferably lyophilized and without preservatives. The amount of major allergens must be known and may vary by manufacturer. Standardized commercial extracts for CAPT that meet all these specifications are expensive, available only in a few countries and for few allergens, which limits the routine use of CAPT in clinical practice. For use, extracts are diluted in saline or diluent, at room temperature, according to the instructions provided by the manufacturer. After dilution, the stability of the solution is guaranteed for 6-24 hours. Mixture of different allergens should not be used.[99]

The reference technique for CAPT was described by Abelson et al.[97] With a metered-dose pipette, 20 40 µL of increasing doses of the diluted allergen extract are instilled into the latero-lower quadrant of the bulbar conjunctiva of one eye, at 15-20 minute intervals, until symptoms of AC occur, when the test is stopped and considered positive (Figure 3). When the maximum dose is applied and no symptoms occur, CAPT is considered negative. The contralateral eye receives only diluent or physiological saline, and serves as a control for the conjunctival reaction in the tested eye. For increasing allergen doses, dilution ratios 10 (eg 1:1000-1-100-1:10) or 2 (eg 1:32-1:16-1:8-1:4) can be used -1:2). Ratio 2 seems to be more appropriate, as it provides progressive dose increases, with more specific, safe and reliable reactions.[99]

The ocular reaction is dose-dependent, with reactions more intense as larger doses of allergen are applied to the conjunctiva, which can lead to clinical symptoms of a late-phase reaction, 6-12 hours after CAPT (Figure 4).[109]

The CAPT is a reproducible test. The minimum interval between two eye challenges should be 7 days. In our study, CAPT was reproducible in 78% of allergic subjects with the same allergen dose that triggered a positive reaction on the first CAPT at 1 week interval, and in 21% with an immediately higher dose.[101] Responsiveness refractoriness to repeated conjunctival challenges at shorter intervals (< 1 week), or often over a prolonged period of time, has been observed.[110] It is possible that the application of increasing doses of allergens at short and regular intervals promotes a decrease in HRCe.[111]

Table 2
Indications and contraindications for Conjunctival Allergen Provocation Test (CAPT)

	Recommendation
Clinic	Confirm the role of the suspected allergen in triggering symptoms in IgE-mediated ocular surface diseases, especially in CAP and when TI is indicated. Define clinically relevant allergen(s) in cases of polysensitization. Clarify cases with a clinical history of AC, but with inconclusive or negative skin and/or serological tests. Diagnosis of occupational (eg latex) or food allergy.
Research	Quantify the antiallergic properties of topical eye medications for AC. Investigate conjunctival allergen tolerance (eg pre- and post-IT). Investigate the pathophysiology of ocular allergic inflammation (mediators, cells, cytokines).
	Contraindication
	Active conjunctivitis (symptomatic patient). Recent eye surgical procedures (3-6 months). History of retinal detachment, Retinal disease, diabetic retinopathy, non-IgE-mediated ocular surface pathology. Pregnancy or lactation. Uncontrolled asthma/Severe systemic disease. Natural allergen exposure (eg pollen season). In use of ocular/oral anti-H1/EC, immunosuppressants, anti-leukotrienes. Contact lenses (must be removed 72 hours before).
Consent	Free, clarified, mandatory.
Presence of the doctor	Mandatory.
Place of realization	Ambulatory or preferably hospital, able to treat emergencies such as acute asthma/urticaria and anaphylaxis, staff trained for the procedure.

CAP = perennial allergic conjunctivitis, CAPT = conjunctival allergen provocation test, AC = allergic conjunctivitis, IT = allergen-specific, immunotherapy, antiH1 = H1 antihistamines, EC = corticosteroids.

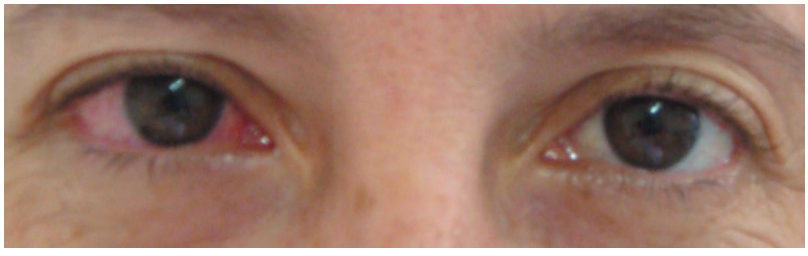
How to evaluate a positive response

There is great variation in the grading of the ocular response during CAPT. To date, there is no universal consensus on a single grading system to be followed.

CAPT is considered positive when it triggers pruritus and conjunctival hyperemia of moderate intensity. Ocular pruritus is the main criterion to be evaluated during CAPT, occurring in 96% of positive tests,[101] and it is recognized by the FDA for evaluating the clinical efficacy of antiallergic drugs and immunotherapy.[99] Spontaneous ocular and periocular itching is the earliest symptom of eHRC, appearing 3-5 minutes after exposure to the allergen, peaking around 10-15 minutes and gradually disappearing after 20 minutes. Conjunctival hyperemia is also a primary sign of eHRC, occurring 5 minutes after allergen exposure, reaching peak intensity at 20 minutes and beginning to disappear after 30 minutes.[101] In our series of eye taunts, Spontaneous pruritus before conjunctival hyperemia was reported by allergic subjects in 66% of CAPT positives with an immediately lower dose of allergen. Some protocols of conjunctival provocation for diagnostic purposes of AC use pruritus as the sole criterion for CAPT positivity.[100]

Due to the subjectivity of the response, since the intensity of pruritus is informed by the patient, it is recommended for CAPT the use of other signs and symptoms of eHRC, such as conjunctival hyperemia, tearing and chemosis, which are evaluated by the physician. These four signs and symptoms are assessed by a cumulative score scale.[97] CAPT is considered positive when the sum of pruritus, hyperemia, tearing and chemosis scores is ≥ 5, with at least 2 degrees of intensity in pruritus and hyperemia (Table 3). This score is calculated before and 15 minutes after the application of the allergen dose to the tested eye. This total score of ocular signs and symptoms can range from 0 to 13 points (Figure 5). Some studies also suggest a complementary score for eyelid edema, which can occur in 53% of positive CAPT.[101]

Efforts have been made to reduce the subjectivity of observations of ocular signs and symptoms during conjunctival provocations such as the use of digital



PROVOCATED EYE
(*L. perenne* - 1:32 dilution)
Total score of signs and symptoms: 9

CONTROL EYE
(Diluent)
Total score of signs and symptoms: 0

Figure 3
Positive Conjunctival Allergen Provocation Test (CAPT) in the right eye

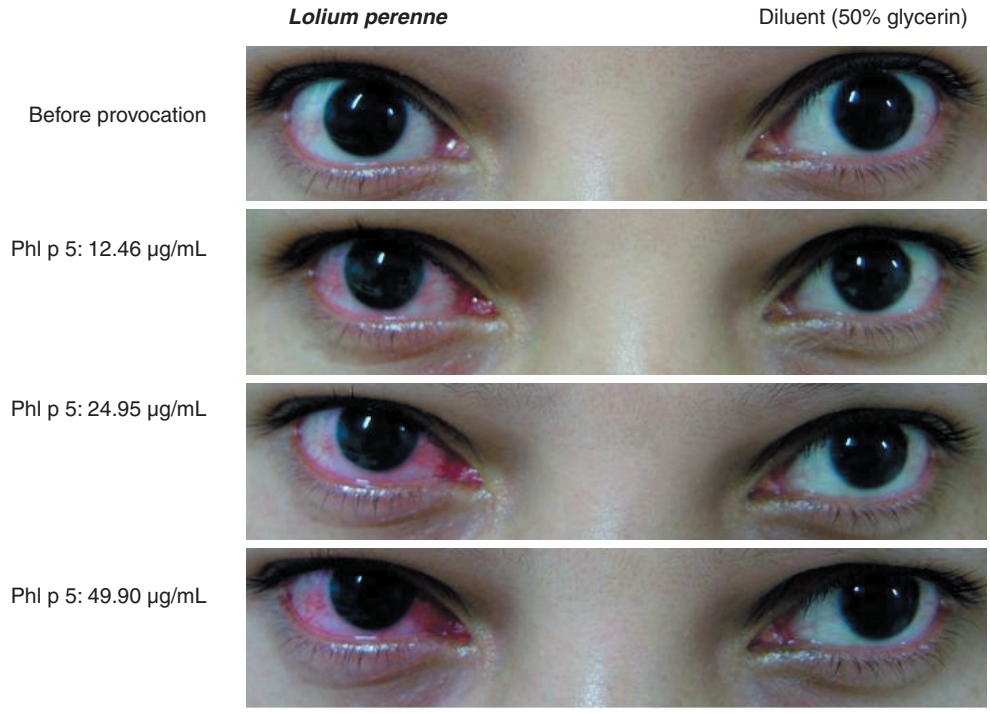


Figure 4
Progression of conjunctival hyperemia with increasing allergen doses during Conjunctival Allergen Provocation Test (CAPT) with *Lolium perenne*. Adapted from Mourão EMM et al.[101]

photography, thermometry, and esthesiometer, but no method has so far been incorporated into the practice of CAPT.[112]

Safety and adverse effects

Although little reported in the medical literature, adverse effects of ocular provocations, such as acute rhinoconjunctivitis, periorbital edema, urticaria, bronchospasm and anaphylaxis, may occur. These reactions are mostly mild and self-limiting, related to the immediate-phase reaction of allergic inflammation.[99]

In a series of 950 eye provocations, there were only two mild systemic reactions in sensitized subjects, one case of late-onset urticaria and one episode of wheezing in an asthmatic subject. One case of anaphylaxis was reported in another study.[97]

In a series of 77 CAPT positive with standardized extracts (Alk Abelló) of *Dermatophagoides pteronyssinus* (83.8 µg/mL of Der p 1), *Blomia tropicalis* (42.4 ng/mL of Blo t 5) and *Lolium perenne* (399, 2 µg/mL of Phl p 5), 88% of the individuals presented nasal itching, sneezing, nasal obstruction and coryza with spontaneous resolution within 1 hour.[113] This occurs by direct drainage of allergens into the nose through the nasolacrimal duct. To minimize allergen absorption and reduce the risk of adverse events, Anderson et al. recommend occlusion of the nasolacrimal duct during CAPT.[114] Eyelid swelling was observed in 53% of CAPT positives. An individual sensitive to *Lolium perenne* developed a late-phase reaction, with intense periorbital edema in the provoked eye (25 µg/mL Phl p 5) lasting 48 hours, requiring oral treatment with corticosteroids and H1 antihistamine. Two other individuals also sensitive to *Lolium* presented moderate swelling of the lower eyelid, lasting for 3 hours even after topical and oral treatment with H1 antihistamine. The challenge

Table 3
Graded scale of signs and symptoms for Conjunctival Allergen Provocation Test (CAPT)

Score	Itching	Hyperemia	Chemosis	Tearing
0	None	None	None	None
1	Intermittent itching	Mild: dilated blood vessels	Light: confirmed with slit lamp	Mild: slightly wet eyes
2	Mild, ongoing eye itching (awareness of the itching sensation, but no desire to rub the eyes)	Moderate: dilated blood vessels	Moderate: Elevated conjunctiva (visible visualization – swollen conjunctiva, especially in the limbus area)	Moderate: occasional rhinorrhea
3	Severe eye itching (constant awareness of the itching sensation but with the urge to rub the eyes)	Severe: numerous and obviously dilated blood vessels)	Severe: bulging of the conjunctiva	Severe: tears running down the face
4	Disabling eye itching (individual insists on rubbing eyes)	Extremely severe: numerous, dilated, engorged blood vessels	Not applicable	Not applicable

Adapted from Abelson MB et al.[97].

doses were 25 and 12.5 µg/mL Phl p 5, respectively. One patient presented severe chemosis at a dose of 12.5 µg/mL of Phl p 5, followed by epiphora and intense ocular pruritus, being treated with an eye patch for 8 hours, oral and topical H1 antihistamines, and topical ocular corticosteroids. All these patients had a papule diameter ≥ 10 mm for *Lolium perenne* on TCA. Also in our study, a controlled asthmatic individual, sensitive to *Blomia tropicalis* (papule diameter ≥ 8 mm on TCA), presented an episode of bronchospasm and shortness of breath with a dose of 28.9 ng/mL of Blo t 5), being treated with aerosol beta 2-agonist, corticosteroid and oral H1 antihistamine.[113]

Although it is considered safe even with high doses of allergens, a potential risk of serious and life-threatening reactions may occur, which justifies the performance of CAPT by a team trained in the method, in a hospital environment or equipped for the treatment of anaphylaxis.[99,100,113]

In conclusion, CAPT is a simple, fast and safe method to evaluate IgE-mediated allergic ocular diseases, especially in cases of perennial allergic conjunctivitis, in polysensitized individuals or when there is no agreement between symptoms and the suspected allergen. With this, we suggest a protocol for carrying out the CAPT, as shown in Figure 6.

Differential diagnosis

Red eye is a common sign and what many consider the "trademark" of all forms of conjunctivitis, although it can also be present by the involvement of other structures of the eye other than the conjunctiva, such as scleritis, uveitis and acute glaucoma (Figure 7).

These include acute and chronic allergic conditions (eg giant papillary conjunctivitis, vernal conjunctivitis, atopic keratoconjunctivitis, upper limbic conjunctivitis, follicular conjunctivitis; infectious causes – eg chlamydial disease, molluscum contagiosum, pirinaud oculoglandular syndrome); and various disorders such as keratoconjunctivitis sicca, acne rosacea, ocular pemphigoid, and blepharoconjunctivitis.[115]

Conjunctivitis in inborn errors of immunity

Inborn errors of immunity (EII), or primary immunodeficiencies (PDI), manifest as increased susceptibility to infectious diseases, autoimmunity, autoinflammatory diseases, allergy, and/or malignancy. To date, there are 430 described genetic defects associated with inborn errors of immunity.[116]

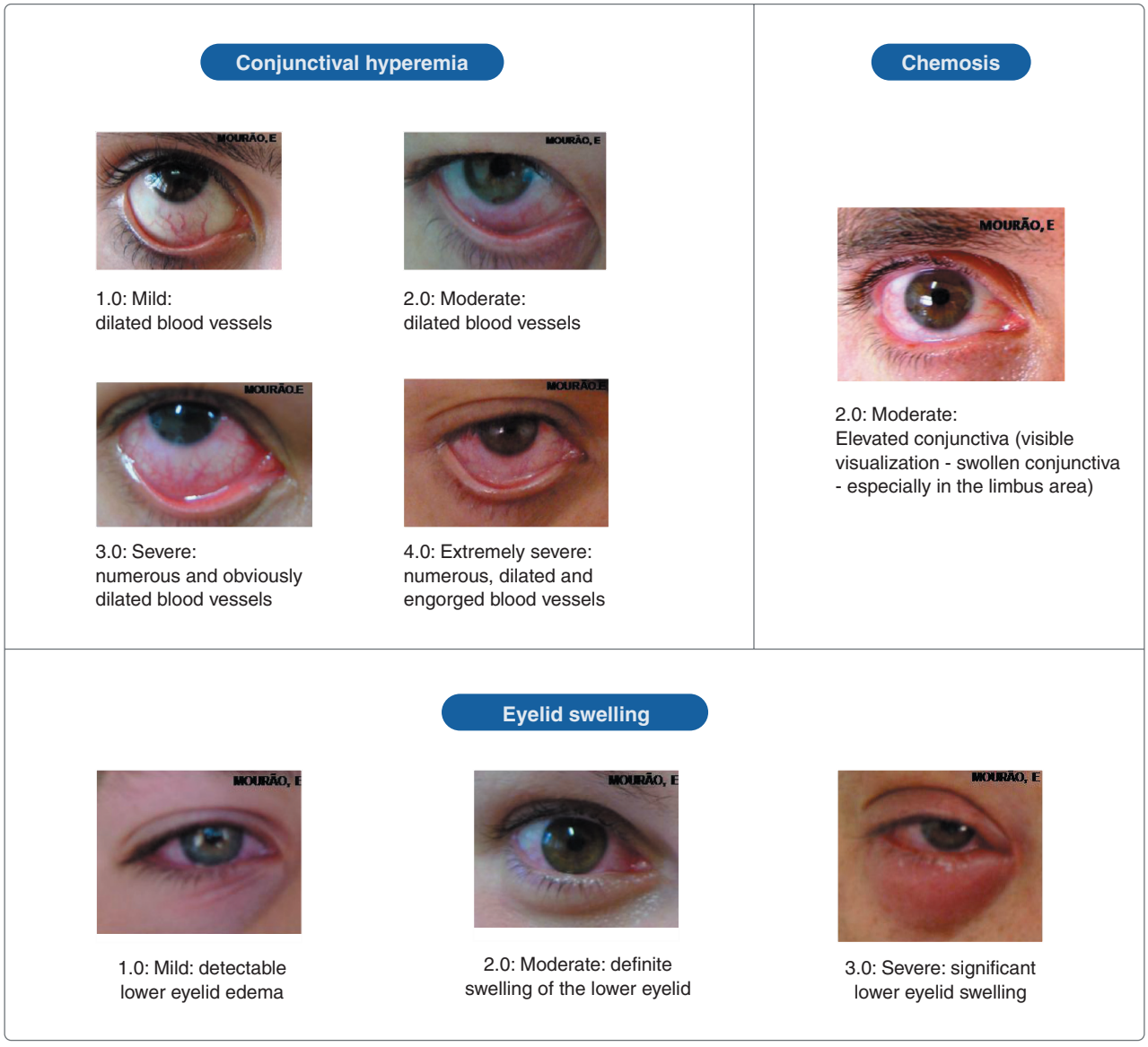


Figure 5
Photographic references during positive Conjunctival Allergen Provocation Test (CAPT)
Adapted from Mourão EMM et al.[101]

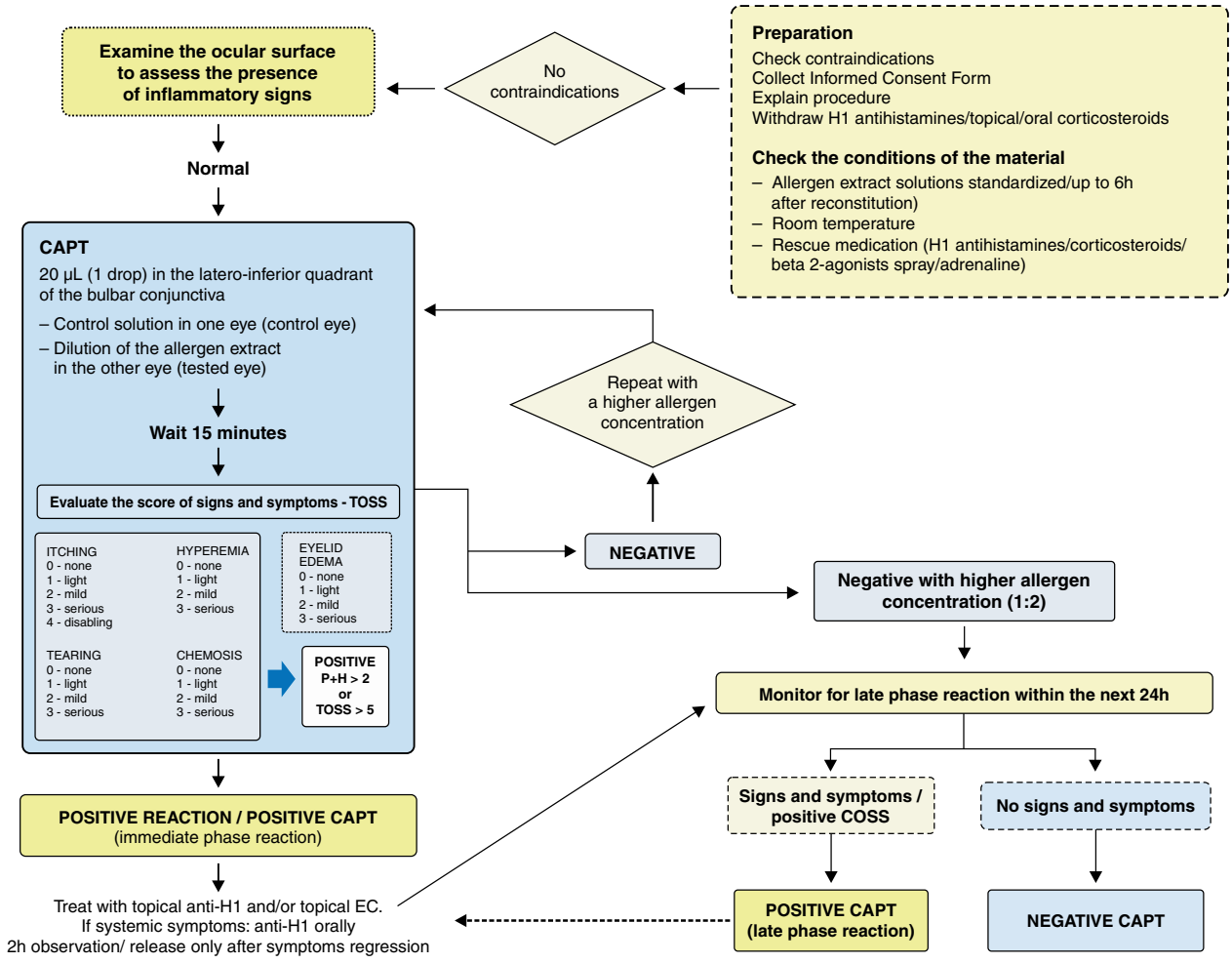


Figure 6
Conjunctival Allergen Provocation Test (CAPT) - Allergic conjunctivitis investigation flowchart

Although ocular involvement is not common, a variety of ophthalmic manifestations may develop and, in some cases, may even precede the typical symptoms of a specific immunodeficiency syndrome.[117]

Knowledge of the mechanisms involved in ocular manifestations in patients with PID allows for early diagnosis and specific treatment, leading to the reduction or prevention of serious visual morbidities.

There are few case reports and few reviews describing ocular manifestations in patients with IIE. In these patients, conjunctivitis may result from increased susceptibility to infections and autoimmunity.[118]

There are few reviews and case reports of conjunctivitis in patients with primary immunodeficiency. A previous study in 90 patients with PID observed a recurrence of non-follicular and non-purulent conjunctivitis in 9% of cases, and a greater predisposition in those with low levels or absence of the main serum immunoglobulins. Among the PIDs associated with conjunctivitis, the main ones were severe combined immunodeficiency, X-linked agammaglobulinemia, and common variable immunodeficiency. The absence of IgA in the tear alone was not a predictive factor for the presence of conjunctivitis or keratoconjunctivitis.[119]

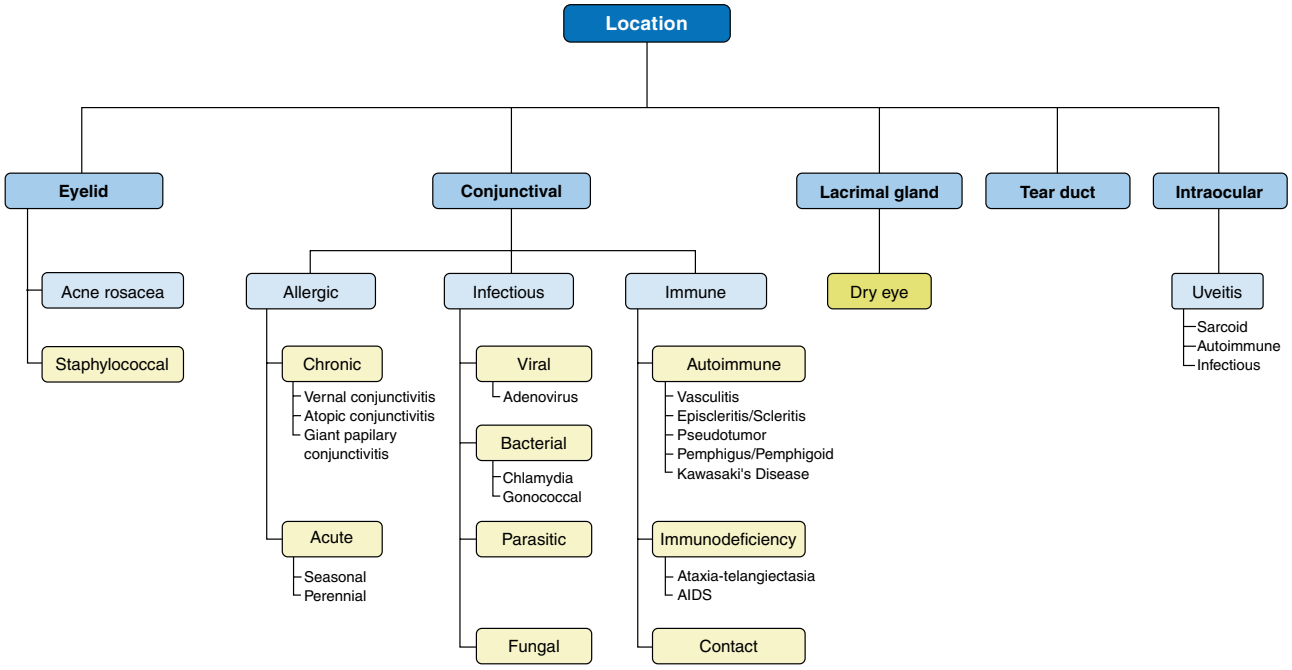


Figure 7
The differential diagnosis of allergic ocular diseases includes a variety of other causes, such as allergic, infectious, autoimmune, and mechanical or nonspecific that trigger the hypersensitivity response of immunologically active extraocular and intraocular tissues. Adapted from Bielory et al.[7]

Severe Combined Immunodeficiency (SCID) is the term applied to the group of rare, serious and fatal diseases characterized by defects in T and B cell responses, resulting in the absence of an adaptive immune response. SCID represents the most severe form of PID, with signs and symptoms that appear in the first months of life, and is characterized by growth retardation associated with recurrent bacterial, viral and fungal infections, including increased susceptibility to infection by opportunistic microorganisms. Most ocular manifestations are a direct result of this susceptibility. Other eye abnormalities described are associated with cytomegalovirus (CMV) infection or after bone marrow transplantation. These findings include chorioretinitis, CMV-associated retinitis, and optic neuritis.[120-122] Opportunistic infections in patients with SCID include toxoplasmosis chorioretinitis, fungal keratitis and endophthalmitis, and conjunctivitis and chorioretinitis caused by *Pneumocystis jirovecii*[119].

X-linked agammaglobulinemia (ALX) is caused by mutations in the gene that encodes Bruton tyrosine kinase (BTK). As BTK plays an important role in the development of B cells, patients with ALX do not generate mature B cells, which results in the absence of plasma cells and, consequently, agammaglobulinemia. Symptoms usually appear early in childhood and consist of bacterial respiratory and skin infections, sepsis, and meningitis. In addition, patients with ALX are susceptible to enterovirus infections and may develop autoimmune diseases. Bacterial conjunctivitis and keratoconjunctivitis due to *Haemophilus influenzae* and *Chlamydia trachomatis* have been observed.[123,124]

Common variable immunodeficiency (CVID) is a heterogeneous, multisystemic disease characterized by hypogammaglobulinemia and poor humoral response to vaccine and other antigens due to

abnormal differentiation of B lymphocytes and/or defects in the interaction between T and B cells. The most important manifestations are recurrent respiratory and gastrointestinal infections, increased incidence of autoimmune diseases and malignancies. Although ocular manifestations in patients with CVID are not common, they may occur due to recurrent infections and autoimmune manifestations. Eye infections can involve all structures in the eye. In cases of bacterial conjunctivitis, *S. pneumoniae*, *H. influenza*e, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and other multidrug-resistant bacteria have been identified.[125,126] Alternative manifestations described in patients with CVID include keratitis, uveitis with granulomatous inflammation, retinal vasculitis, choroiditis, bilateral optic neuritis and chorioretinitis.[127]

Immunoglobulin A (IgA) deficiency is the most common PID, and most patients are asymptomatic. Despite this, there is an increased incidence of autoimmune diseases and recurrent respiratory and gastrointestinal infections. In patients with IgA deficiency, eye diseases have rarely been described, and may affect mainly the conjunctiva.[128]

Isolated IgM deficiency or selective IgM deficiency is a rare primary dysgammaglobulinemia defined by an IgM level of less than 20 ng/dL in children, less than 2 standard deviations below normal in adults, and normal levels of other immunoglobulins. A high frequency of pulmonary manifestations, including recurrent upper respiratory tract infections, asthma and allergic rhinitis, has been described. Some ophthalmic manifestations of selective IgM deficiency, such as recurrent hordeolum, conjunctivitis, and *Staphalococcus aureus* blepharitis, have been documented.[129]

Chronic granulomatous disease (CGD) is a hereditary disease, with X-linked or autosomal recessive inheritance, in which phagocytes are unable to generate reactive oxygen compounds to fight catalase-positive organisms. As a result, patients with CGD are prone to recurrent bacterial and fungal infections. In addition, CGD are associated with an increased risk of autoimmune diseases. Blepharoconjunctivitis has been consistently described in patients with CGD, and can result in punctate keratitis and panus formation.[130-132] Other ophthalmic manifestations in CGD include uveitis[133], candida glabrata keratitis, ulcerative keratitis with limbus granuloma formation, retinal detachment, optic nerve pallor, and corneal ulcers and scarring.[130,131]

Leukocyte adhesion deficiency (LAD) type 1 is an autosomal recessive disorder caused by abnormal expression of Beta 2 integrin (CD11/CD18) on leukocytes. The main clinical manifestations of LAD-1 include late fall of the umbilical stump, recurrent bacterial infections, periodontitis and poor wound healing. Ocular manifestations have been described in a few cases, including eyelid cellulitis, conjunctivitis[134] and medial surface necrosis caused by *Pseudomonas aeruginosa*.[135]

Chronic mucocutaneous candidiasis (CMC) encompasses a heterogeneous group of diseases characterized by recurrent or persistent candidiasis of the skin, mucous membranes and nails. CMC can occur as an isolated symptom, but it is often accompanied by systemic diseases such as Autoimmune Polyendocrinopathy, Candidiasis, Ectodermal Dystrophy (APECED). Recently, several genes related to the generation of IL-17 and IL-22 have been identified and their mutations result in autosomal recessive CMC (CARD9, DOCK8, IL17F, IL17RA) or autosomal dominant CMC (STAT3 mutations and STAT1 gain of function). An underlying immunological abnormality is responsible for the impairment in T lymphocyte function, which results in an inability to produce cytokines such as IL-17 and IL-22, which are essential for the expression of cell-mediated immunity against candida. bilateral keratitis, Keratoconjunctivitis and corneal changes are the most common complications in APECED caused by mutations in the autoimmunity regulatory gene and APECED-like syndromes. Dry eye, blepharospasms and photophobia can be direct results of keratitis. Corneal changes characterized by ulcers, scars and stromal vascularization can affect visual acuity. Keratitis may precede endocrinopathies.[136] Other ophthalmic abnormalities associated with CMC include lens opacities, bilateral iridocyclitis, retinal detachment, optic atrophy, retinitis pigmentosa, anisometric amblyopia, myopia, and reduced tear production. Loss of eyelashes and eyebrows has been attributed to chronic infection with candida or alopecia areata.[137]

Chediak-Higashi syndrome (CHS), a rare autosomal recessive immunodeficiency caused by mutations in the LYST gene, is characterized by abnormal granule formation in neutrophils and melanocytes. Characteristic clinical findings include partial oculocutaneous albinism, severe immunodeficiency, coagulation defects, and progressive neuropathy. Patients affected with this syndrome often suffer

from recurrent bacterial infections. Ocular albinism is considered the main visual manifestation in patients with CHS, who suffer from photophobia and nystagmus.[138] Oculocutaneous albinism is seen in some other PIDs, such as Griselli syndrome type 2, Hermansky-Pudlak syndrome type 2 (HPS2), and p14 deficiency.[139]

Ataxia-telangiectasia (AT) is an autosomal recessive, neurodegenerative disease due to mutations in the ATM gene, characterized by cerebellar ataxia, progressive neurological impairment and telangiectasia. Other characteristic manifestations include immunodeficiency causing sinopulmonary infections, predisposition to malignancies, increased radiosensitivity, and sterility. Ocular manifestations are classified as conjunctival telangiectasia and eye movement disorders. Telangiectasias or twisted and dilated vessels, the second prominent feature, are seen in the bulbar and palpebral conjunctiva and conjunctival fornix. They typically appear later at age 3-6 years compared with ataxia, but are occasionally seen earlier, particularly in children with a positive family history.[140] Such vascular diseases do not cause ocular dysfunction.

Bloom syndrome (BS) is a rare autosomal recessive disorder with DNA repair caused by mutation in the BLM gene. BS is characterized by short stature, facial skin erythema, hyper- and hypopigmented skin lesions, immunodeficiency, hypogonadism, and an increased incidence of malignancies and diabetes. Eye-related pathology is highly variable and may include early-onset retinal drusen (described primarily as colloid body-like spots), telangiectatic erythema, which may extend to the eyelids and bulbar conjunctiva, conjunctivitis, unilateral retinoblastoma, loss of eyelashes, iris pigment and subcapsular lens opacities. Nonproliferative diabetic retinopathy accompanied by hemorrhagic retinitis due to acute leukemia and bilateral optic nerve hypoplasia has also been reported.[141]

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency characterized by the triad of recurrent bacterial infections, eczema, and bleeding diathesis associated with congenital thrombocytopenia and small platelets. Patients are at increased risk of developing autoimmune manifestations and malignancies. Ophthalmic complications are consequences of bleeding diathesis or increased susceptibility to infections, and include conjunctivitis, blepharoconjunctivitis, conjunctival and corneal ulcers, episcleritis, ulcerative keratitis, necrotizing eyelid eruptions, and eyelid eczema. Molluscum contagiosum and herpes simplex viruses are associated with blepharoconjunctivitis.[142] Acute retinal necrosis related to varicella zoster virus presents as diffuse uveitis, retinal vasculitis, and acute retinitis, and can cause serious visual sequelae. Platelet dysfunction can cause eye hemorrhage such as periorbital bleeding, conjunctival, subconjunctival hemorrhage, retina hemorrhage, optic disc hemorrhage, and vitreous hemorrhage.[142]

Treatment

Non-pharmacological treatment

General measures

Nonpharmacological treatment of allergic conjunctivitis includes general measures that are useful for most patients. Patients and/or caregivers should receive educational support about the expected duration and prognosis of ocular allergy, and possible complications from inadequate disease control.

Basic vision care

Patients should be instructed not to rub their eyes, as friction can cause mechanical degranulation of mast cells and worsen symptoms. The application of artificial tear drops or eye solutions without preservatives are useful to dilute and remove antigens from the ocular surface, reducing the concentration of mediators in the tear film, and consequently the allergic symptoms. On the other hand, frequent washing of the eyes with running water should be avoided as it can reduce the stability of the tear layer.[143]

Although the application of artificial tears and cold compresses have no prophylactic effect on the ocular allergic response, these procedures can attenuate ocular signs of inflammation, such as conjunctival hyperemia and increased ocular surface temperature, especially during an acute episode of allergic conjunctivitis. A study involving controlled exposure to grass pollen in patients with seasonal allergic conjunctivitis (SAC) showed that the combination of application of artificial tears and cold compresses, in conjunction with antihistamine eye drops, was superior to the use of medication alone for reducing time and intensity of symptoms.[144]

Generally speaking, patients should reduce or discontinue contact lens wear during symptomatic periods, due to the propensity of allergens to adhere to contact lens surfaces. Lens cleaning

agents, along with storage and rinsing solutions should be preservative-free, as hypersensitivity reactions to these substances can contribute to the inflammatory reaction. Homemade saline solutions are not recommended because of the risk of bacterial contamination.[145]

These measures are especially useful in patients with giant papillary conjunctivitis (GCP) triggered by contact lenses, whose primary treatment is based on removing the source of mechanical irritation. In this case, improving cleaning and storage of lenses to avoid adherence of antigens, reducing wearing time, increasing the frequency of replacement and changing the type and/or model of the same are important auxiliary measures of pharmacological treatment.[146]

Environmental control

The identification of specific allergens for each case and the establishment of inherent measures for their prevention are important steps for the adequate approach to ocular allergy. Likewise, actions that minimize exposure to non-specific triggers, such as exposure to sun, wind and salt water, such as the use of sunglasses, hats with visors and swimming goggles, should be implemented.

As most often allergic conjunctivitis is associated with rhinitis, preventive measures must address both pathologies. Thus, in patients with perennial allergic conjunctivitis (PAC) due to house dust mites, special attention should be paid to the bedroom, which should be well ventilated and sunny. Dust reservoirs such as upholstered furniture, curtains and heavy rugs should be removed or vacuumed at least weekly. Floors should preferably be washable (ceramic, vinyl and wood), and blinds should be blinds or made of material that can be cleaned with a damp cloth. Additional measures include replacing pillows, blankets and mattresses made of kapok and/or feathers with foam, fiber or latex, regularly washing bedding and blankets with detergent and high temperatures (> 55 °C), drying in the sun or air warm and use waterproof covers for pillows, duvets, and mattresses.[147,148]

When the main allergens involved are the epithelium of fur animals, their presence in the room and especially in the patient's bed should be avoided. If it is not possible to restrict the animal to a single area of the house, it is recommended to use Hight Efficiency Particulate Air (HEPA) type purifiers.[147,148]

Preventive measures to reduce the symptoms of seasonal allergic conjunctivitis (SAC) produced by pollens, present in temperate countries and also in southern Brazil, include reducing outdoor exposure, especially in periods of high pollen counts, between 5 and 10 am and on dry, hot and windy days. Windows in homes and cars should remain closed during peak pollen seasons and, if possible, ventilation systems in homes and cars should be equipped with special filters to prevent these allergens.[143,147,148] Additional measures include regular inspection of the environment to reduce sources of moisture and the extermination of cockroaches, in addition to avoiding non-specific irritants, especially cigarette smoke, insecticides, perfumes and deodorants,

Pharmacological treatment

Pharmacological treatment regimens include the use of therapeutic agents, such as oral or topical agents, including antihistamines and, if necessary, topical decongestants, mast cell stabilizers, multi-acting agents, and anti-inflammatory agents.

Oral antihistamines may offer relief from eye allergy symptoms but have a prolonged onset of action. Second-generation H1 antagonists cause less sedation and less anticholinergic (dry eye) effects than first-generation ones.[149] Drugs with dual antihistamine and mast cell blocking activity provide the most advantageous approach in the treatment of allergic conjunctivitis, with symptomatic relief, rapid onset of action and disease-modifying action. In general, children do not like topical ophthalmic preparations, as they often complain of stinging or burning. It is important not to contaminate topical eye medications if the applicator tip comes into contact with the eye or eyelid, or uses one bottle for multiple family members (especially with potential for COVID-19 contamination). Topical decongestants act as local vasoconstrictors, reduce erythema, vascular congestion, and eyelid edema, but have no effect in preventing the allergic response or pruritus as a primary symptom. Chronic use of topical vasoconstrictors leads to tear film instability and conjunctival irritation, with subsequent burning or stinging and even rebound hyperemia. The term “drug conjunctivitis” has been described by the chronic overuse of topical vasoconstrictors in the eye.[150] The combined use of an antihistamine and a vasoconstrictor has been shown to be more effective than the use of either agent alone. Use of topical nasal corticosteroids for allergic rhinoconjunctivitis decreases eye symptoms, presumably via a naso-

ocular reflex and more effectively for seasonal allergic conjunctivitis than perennial forms of allergic conjunctivitis. The effects of long-term chronic use of nasal corticosteroids on ocular symptoms have not been well studied, therefore, they should not be used for the treatment of ocular allergy in the absence of nasal symptoms.[7]

Leukotriene receptor antagonists are useful in the treatment of allergic rhinitis, and although they have been shown to decrease conjunctival nitric oxide levels, their use for ocular allergy is limited.[147,151]

Non-steroidal anti-inflammatory drugs block the enzyme cyclooxygenase and the production of prostaglandins from arachidonic acid. They reduce ocular symptoms, however, they can cause systemic reactions, discomfort on instillation and, occasionally, corneal perforation; therefore, its use must be monitored. Ketorolac is a presentation available for topical ocular use.[150]

Topical (or rarely oral) corticosteroids can be used for the most severe acute cases that require 3-5 days of therapy. Chronic steroid use for eye disorders should only be undertaken in conjunction with an ophthalmologist. Local administration of topical corticosteroids may be associated with increased intraocular pressure. There are some forms of prodrugs, such as loteprednol, which have been shown to have minimal effect on the development of increased intraocular pressure or cataracts. However, all topical steroids can predispose to viral infections and should be used with caution, especially if the patient has a suspected history of viral exposure or unilateral conjunctivitis. Immunomodulatory medications, such as topical tacrolimus or topical cyclosporine, are used as steroid-sparing agents and do not have an adverse effect profile when compared to steroids.[152] Table 4 provides an overview of eye allergy treatment.

Immunosuppression

Topical immunomodulation

Topical calcineurin inhibitors are the most frequently used treatments as corticosteroid-sparing agents in corticosteroid-dependent VKC and AKC. Two systematic reviews on the use of topical cyclosporine (CsA) in VKC and AKC[154,155] showed that topical CsA is effective in alleviating the signs and symptoms of VKC and AKC, reduces dependence on topical corticosteroid eye drops, while maintaining safety similar to of placebo.[154] The second study highlighted the relative paucity of randomized controlled trials evaluating the efficacy of topical CsA in AKC, and suggested that CsA provides clinical and symptomatic improvement and may help to reduce the use of steroids in steroid-dependent or non-steroid-responsive patients.[155]

Cyclosporin A (CsA) is the first topical immunomodulator used for the treatment of severe VKC since the 1990s.[156] Already at that time, CsA was considered an effective substitute for corticosteroids, with excellent anti-inflammatory activity in patients with corticosteroid-dependent and corticosteroid-resistant VKC.[156] CsA is lipophilic and therefore must be dissolved in an alcohol-oil base. For many years, the unavailability of a commercial topical CsA preparation and technical difficulties in dispensing eye drops prevented its widespread use for the treatment of VKC. The 2% formulation was first used in the treatment of VKC, but lower concentrations (1%, 0.5%, 0.1%, 0.05%) were used and proved to be effective for the treatment of moderate VKC to severe.[157,158] When necessary, additional topical corticosteroids may be used in short courses. Systemic absorption was not detected by laboratory methods,[159] which excludes the possibility of local or systemic side effects from CsA. Burning and irritation are frequent side effects, but it is rarely necessary to stop taking the drug. The treatment can be prescribed seasonally or perennially, reducing the doses in the non-active phases of the disease. Adverse events such as bacterial or viral infections are rare, while changes in intraocular pressure have not been reported. but it is rarely necessary to discontinue treatment with the drug. The treatment can be prescribed seasonally or perennially, reducing the doses in the non-active phases of the disease. Adverse events such as bacterial or viral infections are rare, while changes in intraocular pressure have not been reported, but it is rarely necessary to discontinue treatment with the drug. The treatment can be prescribed seasonally or perennially, reducing the doses in the non-active phases of the disease. Adverse events such as bacterial or viral infections are rare, while changes in intraocular pressure have not been reported.

CsA 1% four times daily significantly reduced signs and symptoms and tear levels of eosinophilic cationic protein in a group of patients with VKC,[160] and was reported as the lowest effective concentration in the treatment of corneal ulcers, with recurrence seen at lower concentrations.[161] The effects of the low concentration of 0.05% CsA are controversial,

but considered to be an effective steroid-sparing agent[162,163] and effective in preventing CVC recurrences.[164] In a prospective observational clinical study in 594 patients, 0.1% CsA was shown to be effective and safe for the treatment of VKC.[165]

Topical CsA 0.1% in cationic emulsion (CE) was recently approved in the European Union and Canada as an orphan drug for the treatment of severe VKC based on the results of the VEKTIS study. The study achieved its primary endpoint, demonstrating the superiority of treatment with CsA-EC 4 times daily and CsA-EC twice daily over vehicle, in an efficacy score over the four-month treatment period. This benefit was driven by a decrease in corneal fluorescein (CFS) score (reflecting less damage to the cornea) and a reduction in the use of dexamethasone as a rescue medication in case of exacerbations. In addition, CsA-CE 0.1% significantly improved patients' quality of life (QOL) as assessed by the specific QUICK questionnaire.[166] Improvements in keratitis, symptoms, and quality of life achieved with CsA-EC during the initial four months of treatment were maintained

Table 4
Eye allergy treatment overview in step-by-step format. Modified from Bielory L et al.[153]

Therapeutic intervention	Clinical rationale	Pharmacological agents	Comments
Primary			
Removal	Effective, simple		> 30% improvement in symptoms
Cold compresses	Decreases nerve stimulation, reduces vasodilation		Effective for mild to moderate symptoms
Lubricating eye drops	Washing	Artificial tear	Extremely recommended, comfortable and safe
Secondary			
Topical antihistamine and mast cell stabilizers	Relief in itching	Olopatadine, ketotifen	Antihistamine and mast cell stabilizer
Topical mast cell stabilizers	Safe and effective	Cromoglycate	Relief of mild to moderate symptoms
Tertiary			
Topical corticosteroids	Alleviation of all inflammatory responses including erythema, edema and itching	Loteprednol	Suitable for short periods. Avoid in viral infections
Immunotherapy subcutaneous or sublingual	Identifies and modulates allergic sensitivity		Adjunct in addition to treating allergic rhinitis
Help			
Oral antihistamines	Slightly effective on itching	Always 2nd generation	It can cause dry eye and worsening symptoms

over the subsequent eight-month follow-up period, with both CsA-EC dosing regimens exhibiting safety profiles favorable to throughout the treatment period, providing further evidence that topical CsA-EC is a viable therapeutic option for children and adolescents with severe VKC.[167]

Tacrolimus is a potent drug similar to CsA in its mode of action, but chemically distinct. A tacrolimus skin ointment is licensed for the treatment of moderate to severe atopic eyelid disease and may have secondary benefits for AKC.[168-170] Conjunctival application of 0.03% and 0.1% tacrolimus ointment was effective, well tolerated, and safe in the treatment of severe allergic conjunctivitis.[169,171] In a multicentre, double-blind, placebo-controlled trial, 0.1% tacrolimus ophthalmic suspension was shown to be effective in the treatment of severe allergic conjunctivitis. The dose was based on the results of a previous dose-ranging study in which tacrolimus 0.1% ophthalmic suspension showed more marked improvement and a similar safety profile compared to 0.01% and 0.03%. Patients treated twice daily for 4 weeks with 0.1% tacrolimus significantly improved signs and symptoms. The most frequent adverse event related to tacrolimus was eye irritation.[172] Demonstrations on the quality, safety and efficacy of the different compounded preparations used in the different clinical studies will be needed before tacrolimus is considered an orphan drug for VKC and AKC.

However, a commercial eye drop preparation is available in Asia with the indication of severe AKC and VKC. One review, with a critically low-quality evidence score, highlighted the benefits of tacrolimus over placebo in two randomized controlled trials and four case series.[173] In a prospective randomized comparative double-masked study comparing the efficacy of 0.1% tacrolimus ophthalmic ointment with 2% CsA showed that both were equally effective in the treatment of VKC.[174] In a second study, patients with CsA-resistant VKC[175] treated with 0.1% tacrolimus showed a significant improvement in clinical scores over 1% CsA. A recent study comparing the effect of topical 0.1% tacrolimus alone or in combination with topical corticosteroids in refractory allergic eye diseases, also showed a potential steroid-sparing effect.[176] In addition, 0.03% or 0.1% tacrolimus skin ointments have been shown to be beneficial in the treatment of eyelid eczema in patients with AKC.[177-179]

In twelve patients treated with topical tacrolimus for an average of 8 years, long-term efficacy was shown in the clinical signs of severe AKC and VKC, although half of the patients were not able to completely discontinue topical corticosteroids over time of treatment. It should be noted that increased intraocular pressure and corneal infections were potential side effects.[180] Therefore, tolerability of topical calcineurin inhibitors is a concern as a burning sensation is frequently reported. Molluscum contagiosum, papilloma virus, and herpes infections are rare but recognized risks.

Systemic immunomodulation

Systemic immunosuppressive treatment can be prescribed in most refractory cases at risk of AKC vision loss. Cyclosporine was the most used drug.[181] Azathioprine and mycophenolate mofetil are alternative options.

Immunotherapy for allergens

The patient with allergic conjunctivitis, when looking for an allergy specialist, is not always satisfied with having to use frequently or daily and even more than once a day, oral or topical medications to control symptoms for a long time. Immunotherapy (IT) is the practice of administering gradually larger amounts of an allergen extract to an allergic individual to ameliorate symptoms associated with subsequent exposure to the same allergen.[182] IT is an effective procedure in the treatment of patients with IgE-mediated allergic diseases to defined allergens.[182,183]

By modifying the biological response, it influences the immune responses initiated by the allergen and partially restores the Th1/Th2 imbalance of the allergic individual B and T lymphocytes, Treg cells, blocking antibodies, IL-10 and other cytokines are involved in the action of IT.[183,184] TI with allergen injections is recommended for patients with IgE antibody-mediated respiratory allergy whose symptoms respond inadequately to therapy recommended by clinical guidelines.[185]

TI, when appropriate, should be used in combination with all forms of pharmacological and non-pharmacological treatment, with the aim of allowing the allergic patient to become asymptomatic as quickly as possible. Several randomized, double-blind, placebo-controlled studies have demonstrated the efficacy, safety, indications and contraindications of IT in the treatment of allergic diseases.[186,187]

Allergen IT is indicated for patients who have disease with a mechanism dependent on IgE

antibodies specific to clinically relevant allergens. Therefore, demonstrating allergic sensitization by a positive skin test, for example, is not sufficient, as about 1/3 of the population tests positive without showing symptoms of allergy.[182,183]

The subcutaneous administration of allergens is the main route of application of IT in the treatment of allergic diseases. Sublingual immunotherapy (SLIT) is an effective, safe and convenient alternative to SCIT.

Meta-analyses have shown that SLIT is a safe treatment, reduces symptoms and the need for medication in patients with allergic rhinitis and asthma. New formulations, such as sublingual dissolving tablets and adjuvants targeted at the oral mucosa, increase the effectiveness of SLIT treatment. Despite convincing studies, further information on the mechanism of action, optimal doses and comparison with conventional subcutaneous treatment is still lacking.[187]

Regarding TI in AC, studies are very limited and unsatisfactory due to the study of one type of eye allergy, assessment of one type of allergen, insufficient follow-up parameters, or small sample size.[188]

TI is a safe and effective method of symptom control and prevents exacerbations and the development of new sensitizations in patients with AC without ocular or systemic side effects. It should be considered as an alternative or even a primary treatment for patients with AC to avoid serious eye problems as a side effect of topical steroids, to reduce or avoid long-term pharmacotherapy, and also to reduce the economic burden of drugs.[147]

There is no significant difference between SLIT or SCIT administration routes to achieve clinical and immunological improvement, so the patient can choose their preferred method of therapy. Seven of the eight articles selected for a systematic review on patients with severe AC recommended the use of SLIT and SCIT to improve ocular symptoms in the treatment of allergic rhinoconjunctivitis.[147]

Two other systematic reviews focusing on ocular symptoms concluded that the evidence was moderate for SLIT and low for SCIT in the treatment of pollen and dust mite allergic conjunctivitis.[189,190]

Vernal keratoconjunctivitis (CCV) is a chronic allergic conjunctival disease mediated by mast cells, lymphocytes and epithelial cells. It appears more in prepubescent boys and improves in the third decade of life. CCV can have seasonal exacerbations: 50% to 60% of patients have a positive aeroallergen skin test. Immunotherapy in this disease has not been well studied, and there is no indication for this treatment. IT for atopic keratoconjunctivitis also has little evidence of benefit.

Subcutaneous IT with *Dermatophagoides pteronyssinus* extract (3 µg Der p 1 per application, for 12 to 16 weeks) in asthmatics with allergic conjunctivitis promoted remission of ocular symptoms in 17 of 19 patients with mild to moderate conjunctivitis, demonstrating the effectiveness and speed of the treatment. onset of action of immunotherapy with standardized extract.[191]

Immunotherapy plays a more important role in the "long-term" control of rhinoconjunctivitis. In allergy sufferers who had asthma and rhinoconjunctivitis when exposed to animal dander (eg, allergen Fel d I), immunotherapy has been shown to improve the overall symptoms of rhinoconjunctivitis and decrease the use of antiallergic medications. Clinical improvement and a reduction in allergen sensitivity was also observed in a 12-month study of immunotherapy using a purified and standardized preparation of *Dermatophagoides farinae*.[7]

Biologicals in allergic conjunctivitis

Omalizumab

It is an anti-IgE monoclonal antibody indicated for the treatment of severe asthma and chronic urticaria. It is a humanized IgG1 capable of selectively binding to free serum IgE, specifically in the Cε3 region of the Fc fragment, preventing IgE from binding to the high-affinity receptor FcεRI of many cell types, including basophils and mast cells, producing a reduction in free IgE, and consequent inability to trigger the release of mediators of these cell types. Furthermore, the reduction of free IgE induces a decrease in the expression of FcεRI on the surface of mast cells, basophils and dendritic cells, which leads to a decrease in allergic inflammation and, ultimately, to a lower production of IgE.

Different studies compared the effect of omalizumab vs. placebo in the treatment of allergic conjunctivitis, showing a significant reduction in nasal and ocular symptoms (red, watery and itchy eyes) in the omalizumab group compared to placebo after 12 and 16 weeks. However, omalizumab has not been studied in the treatment of allergic conjunctivitis outside of allergic rhinitis research.[147,192,193]

There are case reports showing a good effect of omalizumab in the treatment of atopic keratoconjunctivitis and vernal keratoconjunctivitis with partial or complete improvement, but in very severe cases in child reports the improvement was not significant or lasting.[194] However, there is no formal indication in ocular allergy.

Dupilumab

Dupilumab is a human monoclonal antibody directed against the alpha subunit of the IL-4 receptor that blocks IL-4 and IL-13 signaling and has demonstrated significant efficacy in patients with moderate to severe atopic dermatitis. Dupilumab is approved for the treatment of moderate to severe AD, asthma with a type 2 inflammatory profile or moderate to severe oral corticosteroid dependent, and chronic rhinosinusitis with nasal polyps. There are no studies reporting its use for therapy of allergic eye disease.

Conjunctivitis has been reported as an adverse effect of this, described as inflammation of the anterior conjunctiva and hyperemia of the limbus. The incidence ranges from 5 to 28% in dupilumab-treated groups compared to 2-11% in placebo groups. Pre-existing allergic conjunctivitis appears to be a risk factor, and dupilumab-related conjunctivitis appears to respond to 0.1% fluorometholone, eye drops, or unlabeled tacrolimus indication in 0.03% ophthalmic ointment.[195] The appearance of scarring ectropion has been reported in one patient treated with it for atopic dermatitis.[196]

Biological agents targeting IL-5, such as mepolizumab, reslizumab, or benralizumab, have not yet been studied in the context of allergic conjunctivitis.

Alternative treatments

Alternative and complementary treatments (CAMs) are called any therapeutic intervention outside the dictates of conventional medicine. Although MACs are used by approximately 80% of the world's population, mostly in Eastern countries, their use is spreading to the West.[197] This increase is based on their low cost, favorable safety profiles, in which they are generally regarded as “natural” treatment alternatives in contrast to the aversion to chronically used drugs (especially corticosteroids) and the sometimes poor outcomes in this chronic disease with conventional therapies. It is noteworthy that despite its widespread use, there are few randomized placebo-controlled studies showing its effectiveness, which makes these alternatives not implemented in international guidelines.[197]

When allergists were consulted about their patients' use of MACs, a high percentage reported that they did. Among them, the most popular were: medicinal plants, vitamins, probiotics, acupuncture, yoga, meditation, body massages, homeopathy, Ayurvedic medicine, etc., to name the most frequent.[198]

Therapy with medicinal plants

Also called phytomedicine or phytotherapy, it uses certain plants that have anti-inflammatory activity.[199]

Butterbur (*Petasites hybricus*): is an herb native to Europe, North Africa and Southeast Asia. In vitro petasins have been shown to inhibit leukotriene synthesis, block histamine binding to H1 receptors, and mast cell degranulation.[200] In a double-blind randomized trial, it demonstrated the same efficacy as cetirizine, with fewer side effects.[201]

Euphrasia (*Euphasia officinalis*): is part of the anthroposophical therapies, very popular in Central Europe. Among its active principles are tannins, flavonoids and phenolcarboxylic acid, which give it astringent, antiseptic and anti-inflammatory capacity. Its use in drops has shown significant effectiveness in reducing eye symptoms, although more studies are needed to determine its usefulness.

Argemone mexicana (berberine, cardose or poppy): is a plant native to America,[202] from which a milky liquid is extracted that contains alkaloids, and has anti-inflammatory and antibiotic effects, which led to its use in the treatment of conjunctivitis.[203]

Lycopus lucidus (Lycopene from China): it is a plant native to China and North America, widely used in Korean traditional medicine. It has compounds that inhibit mast cell degranulation, reducing immediate allergic reactions.[204]

Flavonoids: they are polyphenolic metabolites widely found in vegetables and fruits that make up the usual diet (citrus fruits, onions, green tea, wines, etc.), with proven anti-inflammatory and antioxidant capacity, with numerous health benefits (arteriosclerosis, obesity, Parkinson's, dementia and allergic diseases, etc.). They suppress leukocyte adhesion and neutrophilic degranulation, decrease histamine release from mast cells and basophils,

and inhibit the production of IL-4 and IL-13, thus acting in allergic diseases. The most studied flavonoids for the treatment of allergic conjunctivitis are quercetin, isoquercetin, and catechin.[205]

Application of extracts of *Artemisia abrotanum L* (has a high content of quercetin), granules of Yupingfeng (a mixture of plant roots widely used in traditional Chinese medicine) and *Perilla frutescens* (mint family) via the nasal or conjunctival route were evaluated by dual studies blind, randomized, evidencing relief of symptoms of allergic conjunctivitis, with good tolerance.[7,205]

Cannabinoids: Stimulation of cannabinoid receptors present in the ocular conjunctiva (CB1 and CB2 receptors) produces an analgesic and anti-inflammatory effect, also reducing intraocular pressure. The use of flavonoids and cannabinoids opens up a number of therapeutic opportunities due to their proven efficacy with few side effects.[205]

Other herbs widely used in traditional Chinese medicine (Biminna, Bu-Zhong-yi-Qi-Tang, Shi-Bi-Li) or Japanese (Sho-seiryu-to) have demonstrated efficacy in vivo, but further studies are needed to corroborate their usefulness. clinic.[206]

Indian ayurvedic medicine

There is literature, although scarce, on the use of Ayurvedic medicine, using a mixture of herbs and compared with placebo or medication. The efficacy and safety of Triyushnadi Anjana and cromolyn drops were compared, and significant improvement was seen in the group using Ayurvedic medicine versus cromolyn, with no significant side effects.[207] Other herbal blend formulas have been tested (Aller-7) and compared with prednisone and ibuprofen, with excellent results in animals, but there is no report of their effectiveness in humans.[206]

Acupuncture

Acupuncture is one of the most widespread forms of traditional Chinese medicine in the world. According to her, the placement of needles in already defined places achieves a redistribution of vital energy (Chi or Chi) that constitutes the organism. It has shown a significant effect in the treatment of allergic rhinoconjunctivitis, improving ocular symptoms and quality of life, when compared to placebo in randomized placebo-controlled studies.[208-210] The American Academy of Otolaryngology and Head and Neck Surgery suggests it as a treatment option in patients who do not wish to use conventional medicine treatments.[211] However, due to potential methodological errors (standardization of sites, technique, etc.) and the lack of availability of double-blind placebo-controlled studies proving their usefulness, it can be concluded that more evidence and better levels of standardization are needed. for the treatment of allergic rhinoconjunctivitis.[206]

Energy medicine

Controlled studies that can demonstrate the benefit of using energy channeling techniques (Reiki, Qigong) are needed, as their role in treating allergic diseases has not yet been demonstrated.[206]

Homeopathy: Homeopathy assumes that if the substance that produces a symptom is incorporated into the body in extremely dilute solutions, the pathology is resolved.[212] Its practice is widespread throughout the world, and there is a large bibliography on its usefulness in the treatment of allergic diseases, although some of these publications have methodological problems that make their comparison difficult. Numerous publications have shown a significant improvement when the administration of homeopathy was compared with placebo or a reduction in the use of antihistamines and anti-inflammatories to treat allergic rhinoconjunctivitis when administered together with them, both in children and adults, and with anti-inflammatory drugs. long duration of therapeutic effect.[213-219] Homeopathic immunotherapy, in which extensive dilutions of allergens (mites, pollens) are provided, has also been shown to be useful in the treatment of allergic conjunctivitis, with a rapid therapeutic response and low cost.[214-220] Despite their widespread use throughout the world, MACs offer an acceptable clinical response, with few side effects and lower cost than conventional drugs, but doses and administration procedures are generally not standardized and the literature in some cases is scarce. and methodologically poor. More quality studies are needed to determine the exact mechanism of action, standardize its doses and provide adequate safety margins.

Probiotics

Recent studies have evaluated the effects of different probiotic preparations on ocular symptoms and quality of life in patients with allergic conjunctivitis. Despite the observed beneficial effects, the small number of studies and patients involved does not allow the generalization of these results.[221,222]

Psychotherapy

Patients with severe forms of ocular allergy such as vernal keratoconjunctivitis (CCV) and atopic keratoconjunctivitis (AKC) may need psychological support due to the impact on quality of life and the limitations imposed by the disease. A collaborative approach between the GP, the specialist, and the psychologist should be considered in these cases.[223]

Control assessment

The goal of treatment in allergic conjunctivitis is to minimize the inflammatory effects associated with the allergic response, providing relief from symptoms and preventing complications associated with prolonged ocular inflammation.[192]

We can define control as the disease state in which clinical manifestations are absent or almost completely resolved with instituted therapy.[224] The evaluation of control is an essential part in the monitoring of chronic diseases, since they improve medical decision-making and, consequently, the treatment of patients. In the case of allergic conjunctivitis, follow-up should be multidisciplinary and carried out, whenever possible, in conjunction with the ophthalmologist. Even so, it is important that the clinical physicians involved in the treatment (specialists and generalists) know how to uniformly evaluate the patient's control without the need for specific tools, often available only in the ophthalmological office. For this purpose, clinical questionnaires were developed, which can be answered directly by the patient (or by their caregiver, in pediatric cases), being short, easy to understand and simple to perform.

Control questionnaires for chronic diseases can be based on objective and/or subjective symptoms, but should ideally also assess the patient's quality of life. As allergic conjunctivitis often occurs in association with other diseases such as asthma and allergic rhinitis, some questionnaires developed for these pathologies also include the control of allergic conjunctivitis. We can mention the RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire),[225] the RCAT (Rhinitis Control Assessment Test),[226] the nasal and extranasal symptoms score (ESN), and the visual analogue scale (VAS). In the latter, symptoms are individually graded on a numerical scale of 0-10 cm and scored by the patient, being considered a simple and practical way of evaluating control, however, it does not consider aspects of quality of life. When applied to conditions associated with allergic rhinitis, symptoms can be graded as: moderate/severe > 5 and mild ≤ 5.[227] In the case of RCAT, there are versions validated and translated into several languages, in addition to specific versions for both adults and children. The document ARIA (Allergic Rhinitis and its Impact on Asthma)[228] only suggests the classification of ocular allergy by grading severity and persistence of symptoms. Severity can be classified as “mild”, “moderate” or “severe”, based on the presence or absence of visual disturbances, impairment in daily activities and other symptoms that generate discomfort (Troublesome symptoms).

However, when we consider the occurrence only of allergic conjunctivitis, the literature is scarce for tools that assess it exclusively. The evaluation of the four main symptoms: hyperemia, pruritus, edema and tearing constitutes a non-validated questionnaire, called TOSS[229] (Total Ocular Symptom Score) and that can, similarly to the ESN, assess severity and monitoring of treatment. The only questionnaire available to assess quality of life was developed for use in children with vernal keratoconjunctivitis, and is called QUICK.[230] This questionnaire grades the frequency of eye allergy symptoms on a 3-point scale (1 - never, 2 - occasionally, 3 - always), but can only be used in a specific eye allergy situation.

Recently, Sánchez-Hernandez et al.[231] validated a questionnaire (Table 5) to assess severity and clinical control of allergic conjunctivitis. This questionnaire assesses: ocular symptoms, visual analogue scale and hyperemia. The evaluation of this last item is performed through conjunctival and limbal hyperemia separately, using the Efron scale[232] (Figure 8).

In addition to the scarcity of clinical questionnaires, the difficulty in grading ocular symptoms also occurs because it is an observer-dependent assessment. For this reason, it is recommended that, regardless of the tool chosen, the physician is used to always using it, knowing its strengths and weaknesses, improving the exchange of information between the members of the multidisciplinary team and benefiting the follow-up of the patient.

In view of the above, there is still a great need to advance in the development of more complete questionnaires, which can measure the severity and control of different types of allergic conjunctivitis and in different age groups,[233] favoring a better monitoring and control of patients with ocular allergy.

Complications of allergic conjunctivitis

Complications depend heavily on the disease phenotype and clinical presentations: seasonal and perennial allergic conjunctivitis, giant papillary conjunctivitis, and blephorallergic contact conjunctivitis, while others are not always explained by exposure to allergens, such as vernal keratoconjunctivitis and atopic keratoconjunctivitis.[234]

There are clinical manifestations associated with this condition with the presence of frequently encountered eye lesions, such as: edema of the conjunctival cul-de-sac, papillae in the tarsal conjunctiva, tear film defect, perilimbic pigmentation, corneal epithelium defect, blepharitis, Trantas, aggregate infectious conjunctivitis and pterygium.[235]

Seasonal allergic conjunctivitis or perennial allergic conjunctivitis are accompanied by hyaline-like tearing, eyelid edema, and chemosis, and depending on the duration of symptoms, the associated complications are infectious, in addition to dry eye syndrome which, although it appears to be a not-so-serious complication, can cause serious damage to the ocular surface, affecting the quality of vision and life of patients, with a high cost of medical care due to the high frequency of consultations and treatments.[235]

Vernal keratoconjunctivitis presents complications such as punctate keratopathy, corneal ulcers, conjunctival infiltrates, and giant papillae in the tarsal conjunctiva in up to 6% of patients. Other possible sequelae are amblyopia and keratoconus, which in severe cases may require corneal transplantation. Giant papillae that do not respond to medical treatment can be surgically removed in case of corneal involvement and shield ulcer with inflammatory plaque, and surgical debridement with or without amniotic membrane transplantation may be necessary. Limbic stem cell deficiency, a rare complication, can be treated with a limbal conjunctival allograft.[236]

In atopic keratoconjunctivitis, we found findings similar to allergic conjunctivitis, with worsening eyelid damage. The addition of chronic inflammatory changes on the ocular surface (corneal scarring and neovascularization) and varied changes in the eyelids and periorbital skin, ranging from mild atopic dermatitis to lichenification. complications: staphylococcal blepharoconjunctivitis and herpes simplex keratitis, cataracts, limbal stem cell deficiency, keratoconus, glaucoma, retinal detachment, and corneal or conjunctival tumors.[236]

Table 5
Control criteria adapted from Sanchez-Hernandez et al.[231]

	Controlled (listed below)	Not controlled (at least 1 present)
Eye symptoms (itching, tearing, visual discomfort)	No symptoms or few symptoms or < 2 days/week	Any intensity > 2 days/week
Analog visual scale	< 5 cm	> 5 cm
Hyperemia (Efron scale)	0-1	2-4

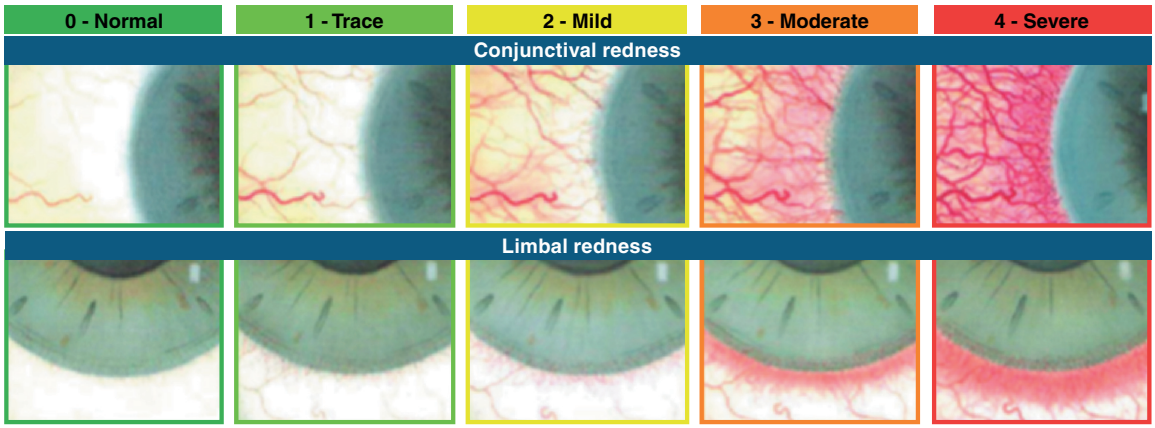


Figure 8
Efron scale

Other complications

One of the most common problems is conjunctival infection; we often find autoinoculating germs, such as *Staphylococcus aureus*, *Hemophilus influenzae* and other streptococci.

Viral infections induce conditions such as acute follicular conjunctivitis, both in children and adults, and the associated viruses are adenoviruses that induce epidemic keratoconjunctivitis and fever, with transmission by direct contact and manifest a week after exposure affecting one of the eyes, and later in both eyes, causing punctate erosions ranging from 1-50 mm with epithelial and subepithelial infiltrate, and management is usually related to the appropriate use of steroids.

Inclusion conjunctivitis is caused by *Chlamydia trachomatis* and is related to sexually active people because it is an oculo-genital disease, as the name indicates that the germ is included in a systemic way, therefore, oral management with macrolides is recommended.

Herpes virus infections also induce follicular conjunctivitis, but occasionally manifestations are few and must be evidenced with fluorescent antibody techniques. Epstein Barr virus infections cause follicular or membranous conjunctivitis with or without hemorrhages, and the symptoms are typical of mononucleosis associated with fever, lymphadenopathy, etc. And when this condition appears, it is very similar to adenovirus keratitis. They may also be associated with other RNA viruses such as Paramyxoviridae, Orthomyxoviridae, Togaviridae and Flaviviridae.

There are complications from chronic eye rubbing. These complications are due to biomechanical processes that are expressed by structural changes of the cornea and ectatic disorders of the cornea such as keratoconus, keratoglobulin and pellucid marginal degeneration, with an evident predominance of keratoconus causing corneal remodeling.

Some of the complications are a result of friction; as an example of glaucoma, since intraocular pressure peaks are related to friction. Another example is dropsy with or without perforation, iris prolapse, lens capsule rupture and intraocular lens displacement, and retinal detachment.[234]

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