

REVIEW ARTICLE

Diagnosing and managing allergic conjunctivitis in childhood: The allergist's perspective

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Abstract

Allergic conjunctivitis in childhood often poses problems of diagnosis and management for the allergist. We present the salient points concerning the diagnosis and treatment of ocular allergy emerging from a large cohort survey conducted jointly in the departments of ophthalmology and paediatric allergy in a French teaching hospital. Seasonal acute conjunctivitis is a common disorder and not overly difficult to diagnose and treat when associated with rhinitis leading to allergic rhinoconjunctivitis. An ophthalmologist should be consulted when conjunctivitis occurs alone and if another form of conjunctivitis is suspected, such as perennial allergic conjunctivitis, vernal keratoconjunctivitis or atopic keratoconjunctivitis. When IgE-mediated hypersensitivity assessment does not establish aetiological diagnosis, a conjunctival allergen provocation test can be performed. The principal non-IgE-mediated allergy is chronic blepharoconjunctivitis. The main problem for differential diagnosis is the presence of signs suggestive of dry eye. Management includes non-pharmacological treatments, such as lacrimal substitutes, avoidance measures and protection of the ocular surface. Second-line treatment consists of eye drops, preferably single dose or without additives and with dual local action, mast cell stabilizer action and antihistaminic action. Third-line treatment is reserved for severe forms. Short-lasting local steroid therapy can control flare-ups of allergic keratoconjunctivitis, which should have specialized follow-up. Cyclosporine is a disease-modifying treatment, which is both effective and well tolerated.

KEYWORDS

allergic conjunctivitis, children, diagnosis, management, ocular allergy

1 | INTRODUCTION

The diagnosis and management of allergic conjunctivitis (AC) involve in the first instance the paediatrician and the family doctor. An ophthalmologist is often called upon, in particular when AC is not associated with rhinitis or when AC symptoms persist or a complication

occurs. An allergist may be needed to establish an aetiological diagnosis and to assist in management and a dermatologist and an ear, nose and throat specialist to eliminate differential diagnoses. Close collaboration between specialists is essential for the proper management of the allergy.

Allergic conjunctivitis is not widely understood for several reasons: (a) the eye has a particular status in the field of allergology, (b) the many debates around the classification of the different forms of AC have been much complicated by ambiguous definitions and terminology, (c) the investigation of AC and therapeutic management are

Abbreviations: AC, allergic conjunctivitis; AKC, atopic keratoconjunctivitis; ARC, allergic rhinoconjunctivitis; CAPT, conjunctival allergen provocation test; EAACI, European academy of allergy and clinical immunology; ECP, eosinophil cationic protein; GPC, giant papillary conjunctivitis; MBP, major basic protein; NAAGA, N-acetyl-aspartyl-glutamic acid; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; SPK, superficial punctate keratitis; VKC, vernal keratoconjunctivitis.

multidisciplinary, and (d) clinical and epidemiological studies of AC are too often compartmentalized or narrow in scope.

The eye is considered as either an open or closed environment. Open to the outside environment, the eye is widely exposed to airborne allergens. In certain cases, investigations for ocular allergy require in situ collection of samples¹ or in vivo challenge of the ocular surface by instilling allergens.² Isolated from the body, the eye may react independently to allergens. Thus, performing a conjunctival allergen provocation test (CAPT) is recommended in certain cases where allergen involvement is strongly suspected despite a negative systemic allergy assessment.

Classification of the different forms of AC has given rise to debate.³ The classification was recently revised by the Interest Group for Ocular Allergy of the European Academy of Allergy and Clinical Immunology (EAACI) (Figure 1).⁴ The resulting publication states that: (a) most cases of conjunctivitis are benign and are associated with IgE-mediated allergic rhinitis: they are either seasonal allergic conjunctivitis (SAC) or perennial allergic conjunctivitis (PAC), (b) severe forms involve the cornea: vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), (c) giant papillary conjunctivitis (GPC), encountered in wearers of soft contact lenses, does not warrant an allergy assessment, and (d) in cases of contact blepharoconjunctivitis (CBC), as for contact eczemas, an assessment of non-IgE-mediated allergy should be made. In VKC, which is considered as an etiopathogenic model of allergic conjunctivitis, conjunctival scrapings found massive infiltration of T cells and especially eosinophils. Multiple cytokines are released in particular TH2 cells induced cytokines.¹ Specific IgE-mediated hypersensitivity was evidenced in at least 50% of cases.⁴ After activation of mast cells, a late phase reaction is frequently in cause, resulting in the release of cytokines responsible for the corneal involvement. Symptoms can also be triggered by non-IgE-mediated factors and also by non-allergic factors.

Investigation and management of allergic conjunctivitis require close collaboration between the ophthalmologist and the allergist ideally in a department that includes specialists from both fields. Only the ophthalmologist can ultimately establish an accurate diagnosis of the clinical form, identify a complication that needs immediate treatment, detect an associated disorder such as dry eye that requires specific treatment, decide on local corticosteroid therapy and oversee its course. The allergist performs a systemic allergy assessment, analyses the relevance of the sensitivities identified by the scientific evidence available and is responsible for appropriate management of the environment.⁵

The epidemiology of AC is poorly documented. It is thought that it could affect up to 25% of children in Europe. A recent study in China reported that ocular allergy had a prevalence of 28%.⁶ In the United States, 20%-30% of the population experience symptoms consistent with a diagnosis of ocular allergy.⁷ In the United States, between 70% and 80% of patients suffering from SAC could have severe ocular symptoms.⁸ The NAHNES study showed that the incidence of ocular allergy has increased over time.⁹ Most cases of AC, in particular SAC, are benign forms. It is estimated that PAC accounts for about 5% of cases of AC. Although in most cases the symptoms

Key Message

This review presents an update on the diagnosis and management of AC in the light of recent publications. The aim is to arrive at a practical application for the allergist based on the recommendations of an expert working in a combined ophthalmology and paediatric allergy department in a university hospital.

reported are mild or moderate, they have a major effect on quality of life.¹⁰ The estimated prevalence in Europe of VKC, which preferentially involves children living in a warm climate, is 3.2/10 000 inhabitants, while complicated forms with severe corneal involvement affect 0.8/10 000 inhabitants.¹¹ This incidence is probably underestimated, as is that of the less common AKC. The proportion of IgE-mediated allergies is high for SAC (95% of cases) but underestimated for PAC and VKC (around 40%-60%).¹² The disparity in

What emerges from our cohort survey: milestones and pitfalls

- Itching eyes is the most common symptom of AC.
- Eversion of the upper eyelid is a simple technique that is easy to perform and provides much information. It contributes to early diagnosis of severe forms of AC.
- The absence of correlation between clinical signs and those observed during the ophthalmological examination.
- The need to establish diagnosis of severe forms (VKC and AKC) as early as possible.
- Non-specific factors such as dry eye are frequently associated to trigger symptoms of persistent forms of AC. They require treatment.
- Ocular rosacea and dry eye are the main differential diagnoses of AC. They do not require allergy investigation.
- For investigation of ocular allergy, less strict criteria of sensitization should be taken into account than in respiratory disorders.
- Immunotherapy is indicated for benign forms of AC when symptomatic treatment is not able to reduce symptoms and improve quality of life. Treatment modalities need to be discussed.
- Local steroid therapy can be used in highly symptomatic forms and for certain complications of severe forms. It requires specialized follow-up.
- High doses of local cyclosporine can be used as disease-modifying treatment for severe keratoconjunctivitis as a steroid-sparing therapy.

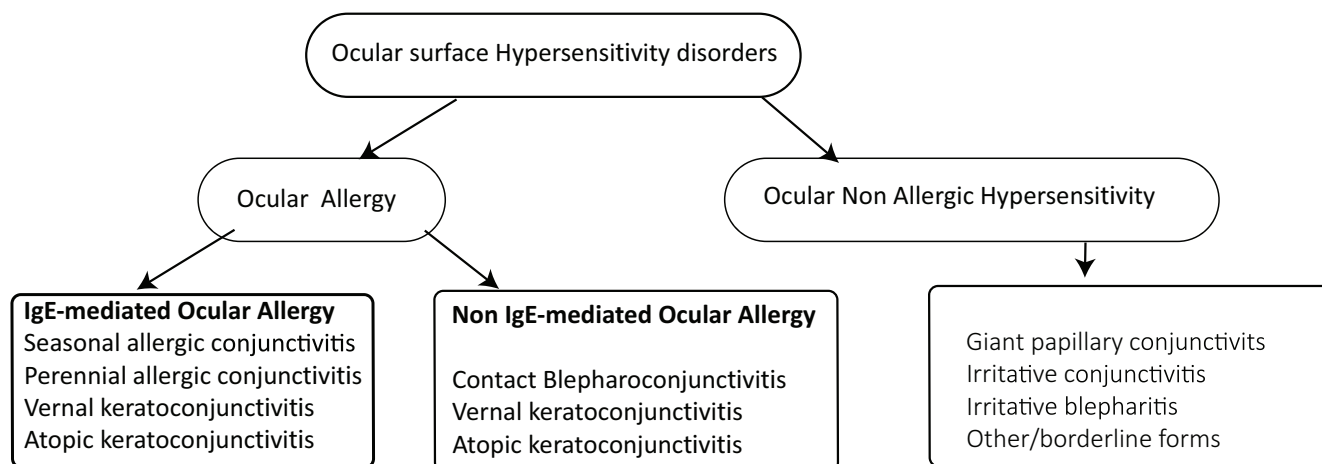


FIGURE 1 Classification of ocular hypersensitivity disorder

the estimated prevalence is due to the small number of surveys conducted, particularly in Europe, and to the method of selection of the populations studied.

This review presents an update on the diagnosis and management of AC in the light of recent publications. The aim is to arrive at a practical application for the allergist based on the recommendations of an expert working in a combined ophthalmology and paediatric allergy department in a university hospital. A full bibliographic search was conducted from the year 2000 to May 2018 on PubMed, Embase and Cochrane databases using the following terms: allergic conjunctivitis, ocular allergy, eye drops, tear, ocular surface, seasonal allergic conjunctivitis, PAC, VKC, AKC. A total of 391 publications, focusing on diagnosis and management, were finally selected.

2 | DIAGNOSIS

The diagnosis of benign cases of AC (SAC and PAC) is generally straightforward (Table 1). Conjunctiva has all the elements required for an allergic reaction, particularly when mediated by IgE (Figure 2). Binding of the allergen to specific IgE leads to degranulation of the mast cells, which are present in large numbers in the conjunctival mucosa.¹³ The release of preformed mediators contained in the storage granules is the main cause of the symptoms of early phase reaction. Histamine binds to the histamine receptors in the conjunctival target cell. It is responsible for allergy symptoms, in particular but not exclusively, eye itching, which is a constant symptom. Histamine produces vasodilation in the area of the conjunctivitis, which in turn triggers other symptoms of immediate hypersensitivity such as watery eyes, eyelid or conjunctival oedema (chemosis), and vascular influx, which causes eye redness.¹⁴ The symptomatology of AC is dominated by these four cardinal signs (TIREd: Tearing, Itching, Redness, Edema). The association with vasomotor rhinitis, the absence of signs of severity (see below) and adverse exposure to allergens are sufficient evidence to establish the diagnosis of AC.

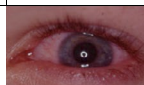



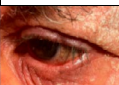
The environmental context will indicate whether its form is acute, seasonal or perennial. Any sign of severity, in particular photophobia, can be detected during clinical examination by a non-specialist. Eversion of the upper eyelid by the clinician is mandatory to rule out more severe forms (Table 2; Figure 3). When the conjunctivitis is isolated, without associated rhinitis, it is preferable to perform a slit-lamp examination to ensure there is no limbal involvement, giant papillae on the tarsal conjunctiva or corneal involvement (superficial punctate keratitis, vernal ulcer or plaque). When other symptoms occur, the ophthalmologist should be consulted to eliminate differential diagnoses such as ocular rosacea and dry eye (Table 3).

The diagnosis of severe cases of AC, VKC and AKC requires the intervention of an ophthalmologist. The severe signs that appear are mainly associated with the late phase reaction of IgE-mediated hypersensitivity (Figure 2). They occur after an antigen-antibody interaction and activation of the eosinophils, which leads to the release of proteins, some of which, such as the major basic protein (MBP) and the eosinophilic cationic protein (ECP), are toxic for the corneal epithelium. Photophobia is predominant among the suggestive signs and points to corneal involvement (Figure 4). There often occur other serious signs, including secretions, eye pain and visual impairment, which are also observed in other diagnoses (Table 3). These signs should prompt referral to an ophthalmologist, in order to confirm diagnosis, rule out differential diagnoses and consider the possibility of local corticosteroid therapy. The ophthalmologist will also investigate for lacrimal dysfunction associated with AC by measuring the break-up time after instillation of fluorescein.

After examination, the ophthalmologist classifies the AC in one of the five entities shown in Table 1.

Seasonal allergic conjunctivitis (SAC) is by far the most common form. It is very often associated with rhinitis. Itching, redness and watery eyes are predominant. The symptoms are triggered by exposure to allergens, with pollen being the most frequently involved. Relapse then occurs regularly at the same time of year. Other allergens, such as animal dander and mould or even some types of food,

TABLE 1 Classification of hypersensitivity disorders of the ocular surface (adapted from Leonardi et al⁴). Adapted from Leonardi et al⁴

	SAC	PAC	VKC	AKC	CBC
					
Presentation	Intermittent	Persistent	Persistent ± intermittent exacerbations	Chronic	Chronic ± intermittent exacerbations
Occurrence	Very frequent	Frequent	Rare	Very rare	Rare
Allergic Mechanism	IgE- mediated	IgE- mediated	IgE and/or non-IgE-mediated	IgE- and/or non-IgE mediated	Non-IgE-mediated
Background	Atopic allergic rhinitis	Atopic	< 10 y ± atopic Male > Female	Adult Atopic	Non-atopic
Clinical symptoms	T.I.R.Ed.	T.I.R.Ed.	T.I.R.Ed. + severity symptoms	T.I.R.Ed. + severity symptoms	T.I.R.Ed. + eyelid involvement
Eyelids	NA	± Palpebral edema	Eyelid edema	Eczema + meibomitis blepharitis	Erythema, eczema
Conjunctival	Follicles &/or papillae	Follicles &/or papillae	Giant papillae	Papillae ± fibrosis	± Hyperemia follicles
Limbus	NA	NA	± Thickened + Trantas dots		NA
Corneal	NA	NA	SPK ± Ulcer ± Vernal plaque ± Opacities, neo-vascularisation		NA
Allergy investigation	Skin prick tests + Serum specific IgE assays				
	± C.A.P.T.				
	Patch tests				
	Tear sampling				
Treatment	First line	Cold compresses/Ocular protection/Allergen and irritant avoidance Lacrimal substitutes			
	Second line	Eye drops: Mast cell stabilizers/Antihistamines H1			
		± Systemic antihistamines			
	Third line	Local steroids*			
		Ciclosporine			
		Immunotherapy			
		Surgical treatments*			
	Psychological support				

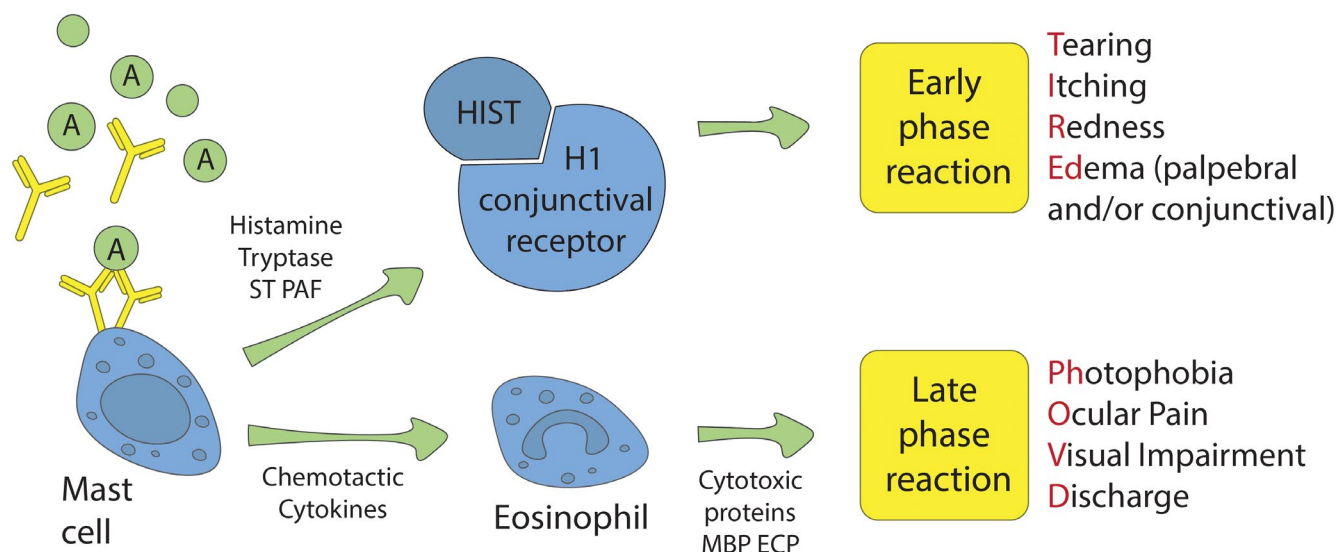
*Under supervision of the ophthalmologist. Bold: Symptomatic treatments.

such as fruit, vegetables, fish, legumes and nuts, can cause acute or recurrent forms, secondary to a systemic reaction after ingestion.

Perennial allergic conjunctivitis (PAC) like SAC is benign but most of the symptoms last longer than 6 weeks. In addition to the hallmark signs mentioned above, there are often signs of non-specific conjunctival hyperreactivity, particularly in an urban setting: the sensation of having sand in the eyes or dry eyes, conjunctival irritation and burning. Clinical examination can show just ordinary papillary conjunctivitis but in the most serious cases SPK can be detected. The allergy assessment should then be focused on perennial allergens such as house dust mites and animal dander.

Vernal keratoconjunctivitis (VKC) is a rare severe form of AC. It serves as an experimental model of the disorder. It affects boys more often than girls, first appears before the age of 10 years and is expressed particularly in warm seasons. Photophobia is a major feature that sometimes causes blepharospasm, intense tearing accompanied by secretions and disabling pruritus. The disorder is

particularly disabling often significantly impairing quality of life,¹² can hamper social life, lead to attention deficiency and even to withdrawal from school. In our experience, we observed no correlation between the intensity of patient symptoms and the signs observed during the ophthalmological examination with a slit-lamp. The examination identifies a palpebral form of the disease with clearly visible cobblestone papillae on the everted tarsal mucosae (Figure 5A) or a limbal form with Trantas dots (Figure 5B) that are sometimes scattered across a limbal ring oedema (Figure 5C), or a combined form. Examination will confirm the corneal involvement indicated by the intensity of photophobia: superficial punctate keratitis (SPK) (Figure 6A), vernal ulcer (Figure 6B) or even vernal plaque (Figure 6C). These evolving complications make it necessary to establish a diagnosis of VKC when symptoms are still moderate, to reduce the quality of life impairment and to avoid visual sequelae. It generally regresses at puberty but certain cases can persist or evolve towards AKC.



A = Allergen; ECP = Eosinophil Cationic Protein; HIST = Histamine; MBP = Major Basic Protein

FIGURE 2 IgE-mediated allergy and ocular allergy symptoms

TABLE 2 How to evert the upper lid?

The patient is requested to look down
Hold the lashes of the patient between thumb and forefinger
Apply a hard surface (tongue depressor, single-dose dispenser) on the outer side of the upper lid
Evert the lid over the hard surface
Look at the palpebral conjunctival mucosa through the lens of an ophthalmoscope

Atopic keratoconjunctivitis (AKC) is even rarer in childhood than the previous entity. It affects individuals with a history of intense atopic dermatitis. They are exposed to the same complications as VKC and later also to tarsal fibrosis and even to symblepharon.

Chronic blepharoconjunctivitis (CBC) is also rare in childhood. It is difficult to diagnose even when associated with eyelid eczema. Diagnosis of CBC is suspected because symptoms are triggered by contact allergens. Local examination provides little information in these cases. There is no associated meibomian gland dysfunction.

The differential diagnosis is established mainly with persistent (PAC) and severe forms of allergic keratoconjunctivitis (Table 3).^{15,16}

- Eye diseases outside the ocular surface pose no diagnostic problem except for certain disorders that cause red eye, which however occur in a very different context and can be diagnosed on the basis of the associated signs. In eye diseases outside the ocular surface, itching, unlike in eye allergies, is rarely a major symptom.
- Non-allergic acute diseases of the ocular surface occur in a different context. In cases of doubt, particularly regarding herpetic

infection (where steroid therapy is contraindicated), an ophthalmologist should be consulted.

- Non-allergic chronic diseases of the ocular surface are the major differential diagnosis: ocular rosacea and dry eye. Ocular rosacea combines meibomian gland dysfunction with meibomitis clearly visible on slit-lamp examination. Cutaneous lesions may also be present. Ocular rosacea requires no allergy assessment.
- Dry eye can be associated in varying degrees with severe and persistent forms of AC. Diagnosis is confirmed if break-up time lasts longer than 10 seconds after staining with fluorescein. In children, the condition is rarely isolated and not sufficiently intense to simulate AC. Likewise for refractive disorders, which, if they are poorly compensated for by vision correction, can induce symptoms suggestive of AC,¹⁷ some patients may have short break-up time and evaporative dry eye, also associated with blepharitis and meibomian gland dysfunction.
- Giant papillary conjunctivitis has become increasingly rare since the gradual phasing out of soft contact lenses. It can develop, however, on surgical thread or ocular prostheses. Previously classified as a form of AC, it does not require a complementary assessment.

The aetiological diagnosis of allergic conjunctivitis in childhood is based on the allergy assessment (Table 1).

In some cases, allergy assessment is not useful: (a) When the AC is acute and not recurrent and its cause is clearly established as, for example, in cases of conjunctivitis secondary to contact with animals. Allergy investigation is also not mandatory when symptoms of seasonal conjunctivitis are mild, do not impair the quality of life and are controlled by a symptomatic treatment. (b) When contact allergy is suspected in cases of blepharoconjunctivitis the allergy assessment consists in a battery of patch-tests. Our experience in children is limited to the use of the European battery

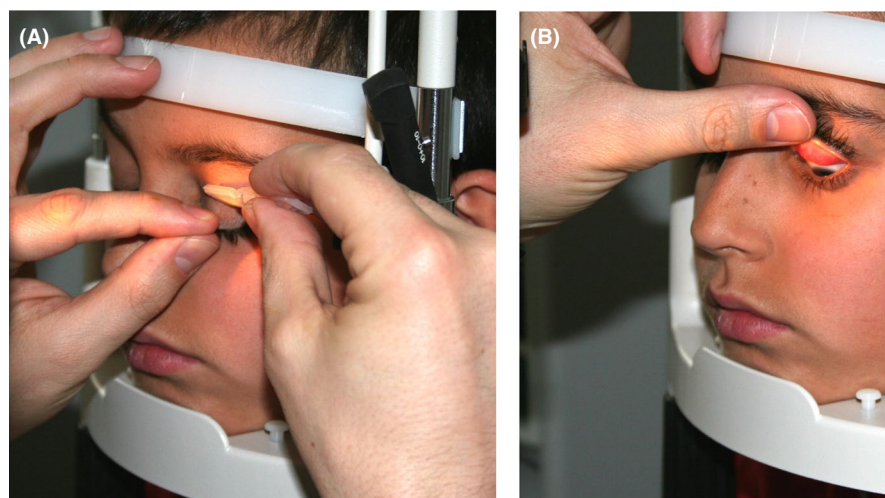


FIGURE 3 Everting the upper lid. A, Technique. B, Giant papillae, seen with the naked eye on the everted lid

of tests, which can be completed by patient use of topic treatments and additives.¹⁸ (c) In most instances, investigation consists of looking for an IgE-mediated allergy, which is involved in about 95% of cases. This approach is all the more relevant when history-taking has shown atopic predisposition (a personal or close family history of atopy) and if analysis of the child's lifestyle, the evolution of the symptoms, the environmental exposure and the efficacy of the treatments point towards the involvement of airway or

food allergens. Clinical examination can provide signs suggestive of nasal, respiratory or skin allergy. Identifying an IgE-mediated ocular allergy is done in two stages: detecting an allergen to which the child is sensitized and confirming the involvement of the allergen in the ocular surface disease.

Investigation of allergen sensitization is based on a thorough oral interview. This standard allergen assessment, which is performed on an outpatient basis, can solve the most common cases.

TABLE 3 Relevant signs related in clinical ocular examination¹⁵

Sign	Sign of severity	Positive association with ocular allergy	Type of allergic conjunctivitis	Differential diagnosis
Signs assessable by a non-ophthalmologist				
Conjunctival redness	No	+	All	Non-allergic conjunctivitis, (epi) scleritis, keratitis, uveitis
Conjunctival giant papillae	Yes	++++	VKC, AKC	GPC
Limbal inflammation	Yes	++++	VKC, AKC	Limbal tumour
Chemosis, lid oedema	No	+	All	Non-allergic conjunctivitis
Mucus discharge	No	++	All, especially VKC, AKC	Infection, severe dry eye, GPC
Lid eczema	No	++++	AKC, CBC, VKC	Seborrhoeic dermatitis, psoriasis, lid molluscum
Blepharitis	No	(Only in AKC)	All	Rosacea, seborrhoeic dermatitis
Signs only assessable by an ophthalmologist				
Conjunctival papillae	No	+++	All	Bacterial conjunctivitis, rosacea, dry eye
Conjunctival follicles	No		All, especially CBC	Viral or chlamydial conjunctivitis, Parinaud's oculoglandular syndrome
Superficial punctate keratopathy, corneal scars, pannus	Yes		VKC, AKC	Non-allergic keratitis
Corneal shield ulcer or plaque	Yes	++++	VKC, AKC	None
Tear instability	Np		PAC > AKC, VKC	Rosacea, non-allergic tear instability

AKC, atopic keratoconjunctivitis; CBC, contact blepharoconjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis.



FIGURE 4 Photophobia

Skin prick tests are systematically carried out. Certain allergens are tested for in all patients and others solely according to the environmental context such as collective housing, tropical climate, the Mediterranean region. Serum-specific IgE assays are prescribed systematically and in addition according to the results of skin tests and the circumstances in which the symptoms appeared (Table 1). These investigations should be able to detect sensitization to airway allergens including house dust mites, animal dander, atmospheric moulds and seasonal pollens from grasses, trees or weeds. We advise food sensitization should be routinely investigated in children although implication of food allergen remains

controversial in ocular allergy.¹⁹ Our experience in ocular diseases and observation of cases in which the assessment was weakly positive but the challenge test (CAPT) strongly positive led us to consider an assessment of ocular disease to be positive if one of the two following criteria was fulfilled: wheal skin test size greater than half of that of the positive histamine control test or specific serum IgE >0.10 IU/mL.

Analysis of the relevance of the assessment is where the allergist's expertise is paramount. It serves to assess the responsibility of the allergen for the symptoms reported. The solution is sometimes easy to find when there is a correlation between an allergen evidenced and exposure to the allergen and the usual manifestations of the disease as, for example, in the case of seasonal AC with intense and isolated sensitization to pollens, or that of recurrent AC occurring in a place where a domestic animal is present. In other circumstances, the solution is not so simple either because the subject is polysensitized or because the relation between sensitization and the symptoms is not clear-cut or because the history-taking suggests the allergy was triggered in a child whose systemic tests were negative.¹² In these cases, a conjunctival allergen challenge (CAPT) should be performed. The Interest Group for Ocular Allergy of the EAACI has drawn up guidelines for standard practice of CAPT (Figure 6A).² The test is used to verify the relation between exposure to the allergen and the onset of symptoms. Topical treatments should be stopped 48 hours before the test and systemic antihistamines 2 weeks before. Precautionary measures, prerequisites, practical modalities and positivity criteria have been described recently.²

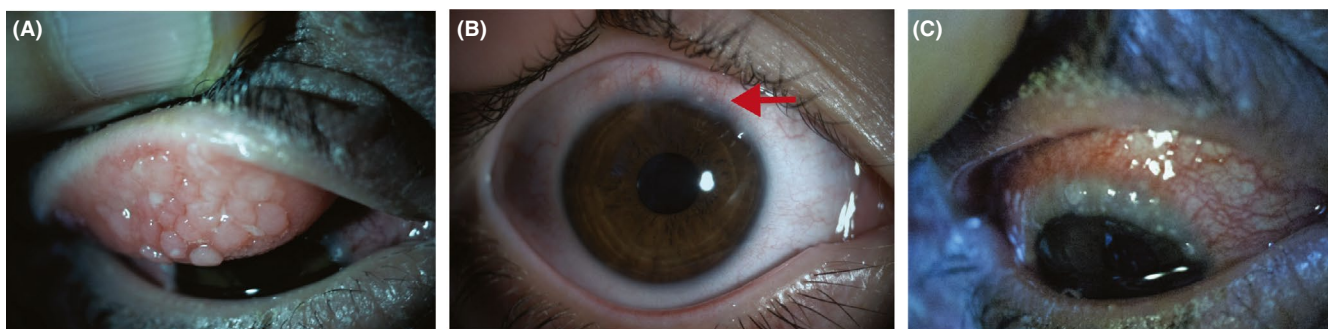


FIGURE 5 Clinical aspects of allergic keratoconjunctivitis vernal keratoconjunctivitis and atopic keratoconjunctivitis. A, Giant papillae. B, Limbal Trantas dot. C, Limbal involvement: limbal oedema, ring and Trantas dots

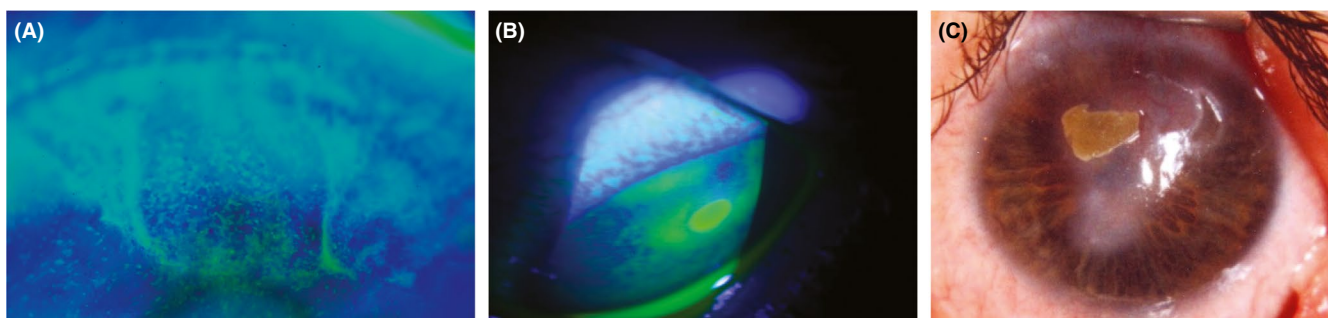


FIGURE 6 Corneal involvement in allergic keratoconjunctivitis: vernal keratoconjunctivitis and atopic keratoconjunctivitis. A, After fluorescein instillation: superficial punctate keratitis. B, After fluorescein instillation: Corneal ulcer. C, Vernal plaque and corneal opacities

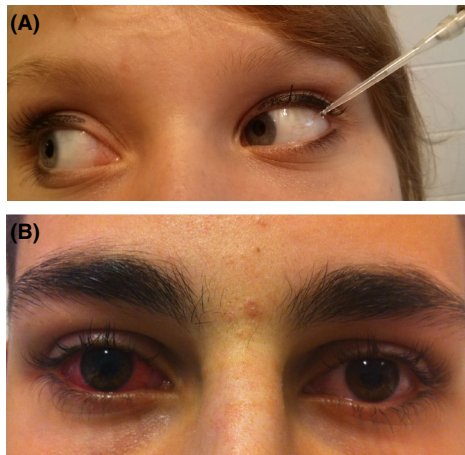


FIGURE 7 Conjunctival Allergen Provocation Test (CAPT). A, Instilling saline (left eye) or allergen (right eye). B, After allergen extract instillation (right eye): positive CAPT to *Dermatophagoides pteronyssinus*

(Figure 7). It can be performed in the hospital for the more severe forms of ocular allergy or in an outpatient setting for benign forms using a simplified scoring system.

Thus, the allergist plays an essential role in the management of ocular allergy. However, in complex cases of keratoconjunctivitis, vernal or atopic, investigation of allergy can warrant further investigations in collaboration with the ophthalmologist.¹⁵ In our practice as a combined team of specialist ophthalmologists and allergists, we use tear sampling to assess IgE-mediated allergy on the ocular surface: presence of eosinophils on a tear drop, eosinophil cationic protein (ECP) assay or quantitative assay of total IgE in the tears.⁵ Interpretation of the results should be made with caution and take into account the possibility of rupture of the haemato-lacrimal barrier. In practice, the difficulties of sampling tears, particularly in children, make the procedure of limited use. There is no firm evidence that techniques using paper strips inserted into the eyes are reliable.²⁰ The presence of allergen-specific IgE in tears is a strong argument in favour of in situ allergy. Assessment of specific IgE in tears using biochips is currently underway. Tears can also be used to quantify the degree of local inflammation by measuring the levels of proteins and cytokines released before and during treatment and which provide information on the mechanisms involved in the diseases.²¹ Conjunctival scraping is less used than impression cytology is of great interest because it can be performed in some children.¹⁵ In severe forms of ocular allergy, that is VKC and AKC, IgE-mediated hypersensitivity should be investigated first, but non-IgE-mediated hypersensitivity should be sought particularly in cases persisting after puberty and in AKC.

The allergens responsible for ocular allergy are predominantly grass pollens and indoor allergens. The EAACI has clearly defined the relations between allergic hypersensitivity and ocular disease (Figure 1).⁴

Pollens are responsible for eye and nose symptoms of allergy. Hay fever is directly related to the period of pollination, which varies according to climate and geographical location. Pollen

counts can therefore play an important part in the optimal management of AC.^{22,23} When pollinosis is due to trees or grasses, the duration of exposure and of symptoms is longer. Certain tree pollens cause food cross-sensitization, which in turn gives rise to allergic reactions that generally are benign. Among other intermittent allergens, moulds such as *Alternaria alternata* can cause AC according to environmental conditions. In fact, any perennial allergen, depending on exposure conditions, can trigger intermittent symptoms. Animal dander can cause intense conjunctivitis in children. Exposure to house dust mites or cockroaches can result in PAC. Numerous non-specific factors can produce hyperreactivity on the ocular surface, with the same symptoms as those of ocular allergic hypersensitivity. Non-specific conjunctival hyperreactivity can be isolated or occur in association with allergic hyperreactivity.¹⁷ There is no definitive technique for evidencing non-specific ocular hyperreactivity.

3 | TREATMENT

There is no consensus about the treatment of AC in childhood. However, the Interest Group for Ocular Allergy of the EAACI recently published an update of the techniques used in management of the disease.²⁴ They concluded that good understanding and cooperation between the family physician, allergist and ophthalmologist are essential for optimal management.

First-line treatments should not be overlooked. Physical treatments can be prescribed in all cases. Patients appreciate the anti-inflammatory effects of cold compresses applied on the eyelids.²⁵ Saline solution eye wash contributes to local elimination of allergens and secretions and the dilution of cytokines released on the ocular surface. Artificial tears can be used in all clinical forms of AC. When they are prescribed for dry eye or a persistent or severe form of AC, they should preferably contain no preservatives and thus be in single-dose formula or with additives that are reabsorbed in the tip of the dispenser. The viscosity of the molecules varies according to whether they are Newtonian (saline solution, vinyl polymers) or not (cellulose derivatives, carbomers, hyaluronate). Gels are less often used to treat AC. Other preventive measures aim to limit contact with non-specific irritants such as pollutants and in particular tobacco smoke. Avoidance strategies should be adopted when possible if an allergen is incriminated in AC. Otherwise, wearing protective glasses is a recommended precaution in addition to protection against ultraviolet light. Wearing contact lenses and the use of facial cosmetics should be avoided as much as possible.

Second-line treatments are local symptomatic treatments that can also be prescribed by a physician other than an ophthalmologist.^{26,27} They are usually able to effectively treat PAC and SAC. Mast cell stabilizers such as sodium cromoglycate, N-acetyl-aspartyl-glutamic acid (NAAGA), nedocromil sodium and lodoxamide are used as curative remedies.²⁸ They have the drawback of needing repeated instillation. Antihistamines exert preventive effects on

the H1 histamine receptor of the conjunctival mucosae. The main molecules are antazoline, pheniramine, levocabastine, emedastine, bepotastine and ebastine. Some molecules have additional mast cell stabilizer effects or effects on the late phase of IgE-mediated hypersensitivity. These dual or triple action eye drops should be accorded priority of use. The main molecules are azelastine, ketotifen, epinastine and olopatadine. The last two molecules are commercially available at various concentrations. Alcaftadine has H4-antihistamine action. Contact allergic reactions to additives can be avoided by using single-dose formulas. Combination with oral H1-antihistamines is recommended when there is associated rhinitis or in case of resistance to local treatment.

Third-line treatments are specialized treatments. In the event of severe signs that can immediately establish the diagnosis of allergic keratitis and in the most severe forms, with a high symptomatic score, the ophthalmologist can prescribe local steroid treatment and recommend specialized follow-up. The protocols are generally short and rapidly degressive. In the short term, their strong efficacy involves the risk of self-medication and in the long-term steroid dependence with the concomitant risk of iatrogenic complications such as cataract and cortisone glaucoma. Topical non-steroidal anti-inflammatory drugs are rarely used because they are not always well tolerated.²⁷ Systemic anti-inflammatory drugs are only exceptionally used to overcome a difficult period in selected cases of severe forms. The ocular effects of nasal anti-inflammatory drugs are considered beneficial in the short term in cases of allergic rhinoconjunctivitis (ARC) but their long-term use has not been validated.^{29,30} The allergist can suggest allergen immunotherapy, in particular in cases of SAC or PAC for which symptomatic treatment is not sufficient to ensure satisfactory quality of life when IgE-mediated allergy and involvement of an allergen have been formally identified. It is important to respect certain modalities when using immunotherapy. Treatment should be initiated outside the symptomatic period at initially low doses and in gradual increments with back-up symptomatic treatment if necessary. A Cochrane meta-analysis showed that sublingual immunotherapy (SLIT) had an overall weak to moderate effect on the symptoms of patients with ARC and AC.³¹ There are no documented reports of the use of subcutaneous immunotherapy for VKC and AKC. Indications should be established case-by-case by a multidisciplinary team according to the evolution of the disease. In severe forms, the use of calcineurin inhibitors has now become common practice. Cyclosporine treatment is available in most European countries. Concentrated at 1%-2% in eye drops, it is well tolerated.³² It is prescribed in cases of keratoconjunctivitis as a steroid-sparing treatment. Other treatments, such as local tacrolimus, have been tried in selected cases.³³ Biotherapies (omalizumab, dupilumab) are currently under study.³⁴ In complicated forms of VKC and AKC, the ophthalmologist can decide on urgent surgical treatments such as supratarsal injection of steroids, abrasion of a vernal plaque or application of an amniotic membrane graft to heal a corneal ulcer.³⁵ In cases of AKC, psychological care and individualized support are instrumental in helping children

severely handicapped by their ocular surface disease to take up or resume their school studies.

In practical terms, the management of AC in children can be summed up as follows (Table 1).

- In cases of non-recurrent acute conjunctivitis, allergy assessment is generally unnecessary and only local treatment is required.
- In cases of acute but recurrent conjunctivitis, an ophthalmological examination should be performed during a flare-up phase to eliminate complications. Local treatment should be accompanied by follow-up. Allergy assessment can be performed after the initial management to guide avoidance and/or to prescribe immunotherapy.
- In cases of persistent AC that is resistant to treatment, the ophthalmological examination can differentiate between benign but persistent forms (PAC), which require assessment and possible immunotherapy, and severe forms (AKC and VKC), which require multidisciplinary management and specialized follow-up.

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