



A Practical Approach to Management of Allergic Eye Conditions in Children

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Introduction

While nasal allergy all along has been important in allergy research, ocular allergy is now increasingly recognized as a distinct symptoms-and-signs complex that imposes significant disease burden with reduction of quality of life of patients. Allergic conjunctivitis is highly prevalent in Hong Kong and has a close epidemiologic relationship with allergic rhinitis.

The emphasis of this article will also be on what a paediatrician can do prior to the point of referral: recognition of the ocular symptoms, recognition of potential sight-threatening situations, and effective initial treatment.

Disease burden

While we are still awaiting published evidence for official incidence of ocular allergy in Hong Kong, a recent survey from the Eye Institute of the University of Hong Kong, conducted during May and June 2009 on 1,000 parents with children less than 12 years old in Hong Kong, has estimated that approximately 30% of children suffered from eye allergy.¹

The incidence of ocular allergy varies in different geographical regions and tends to be more common in countries with warm climates. In the US, as much as 40% of the general population suffered from allergic conjunctivitis.²⁻⁴ In one study of 5000 allergic children, 32% had ocular symptoms as the single manifestation of their allergies.⁵ A recently published prevalence study in Japan has found that out of 1079 patients with allergic ocular disease, the seasonal and perennial allergic conjunctivitis consist of over 90% of all cases, with a much higher mean age of over 50 years old and a less severe overall clinical score than the chronic types such as vernal and atopic keratoconjunctivitis.⁶

In USA, expenditure related to ocular prescription medication rose from US\$6 million in early 1990s to >US\$200 million in the new millennium, projecting an annual growth of 25% per year in USA.⁷

Classification

BASIC IDEAS – CLASSIFICATION^a

- 1. Seasonal allergic conjunctivitis **SAC**
- 2. Perennial allergic conjunctivitis **PAC**
- 3. Vernal keratoconjunctivitis **VKC**
- 4. Atopic keratoconjunctivitis **AKC**
- 5. Giant papillary conjunctivitis **GPC**
- 6. Contact allergy (Toxic conjunctivitis)

a. Calonge M: Classification of ocular atopic/allergic disorders and conditions: an unsolved problem. *Acta Ophthalmol Scand Suppl* 1999;(228):10-3

SAC and PAC are more common, and while they are symptomatic, they are less likely to result in long term ocular complications. VKC and AKC are rarer, more chronic but are potentially associated with severe blinding ocular complications. **One key task the patients and ophthalmologists would appreciate, will be for our paediatricians colleagues to look out for VKC and AKC and refer them to eye care.** GPC typically occurs in contact lens wearer, and contact allergic conjunctivitis can be diagnosed on history of, for example, chemical exposures.

Highlights in pathogenesis

In all forms of allergic eye diseases, the clinical response is mainly caused by the mast cells activation due to either an antigen – mast cells linkage or T-cell activation of mast cells. The activation of conjunctival mast cells in turn leads to the release of histamine,

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prostaglandins D2, leukotriene C4, tryptase, chymase, platelet activating factor (PAF) and other chemoattractants. This further attracts the eosinophils and neutrophils.⁸⁻¹¹ Vernal keratoconjunctivitis and atopic keratoconjunctivitis are traditionally seen as type I IgE-mediated hypersensitivity reaction. However current evidence shows that eosinophils and its major basic proteins are also important players in the chronic allergic process, with its role in eliciting ocular surface inflammation and epithelial damage.¹² The chronic allergic conjunctivitis has an increased concentrations of T helper-1 (Th1) and especially T helper-2 (Th2) cells, which stimulate the migration and proliferation of conjunctival fibroblasts as well as protecting these cells from apoptotic cell death, effects that likely underlie the hyperplasia of fibroblasts, contributing to the formation of giant papillae. Stimulation of fibroblasts in the corneal stroma with the combination of a proinflammatory cytokine and either IL-4 or IL-13 results in up-regulation of the expression of the chemokine eotaxin and thymus- and activation-regulated chemokines as well as of vascular cell adhesion molecule-1, which together mediate the infiltration and activation of eosinophils and Th2 cells.¹³ Fibroblasts therefore appear to play a central role in the induction and amplification of ocular allergic inflammation and the consequent development of giant papillae and corneal disorders in individuals with VKC.

Acute allergic conjunctivitis

Acute allergic conjunctivitis (AC) is the commonest form of allergic eye diseases. It can be divided into seasonal (SAC) and perennial (PAC), with PAC considered as a chronic variant of SAC. In most cases, allergens can be identified. Patients usually present with acute ocular symptoms such as itchiness, tearing, ocular irritation and discomfort. The symptoms are usually short lived and are not tend to be recurrent. Classical signs include redness, injection, lids swelling and chemosis. Bilateral signs and symptoms are common. Allergens that can initiate these symptoms include dust mites, pollens and fungi, the presence of which suggests a seasonal variation pattern. Patients usually have a history of atopy, asthma and allergic rhinitis.

One key issue is how to differentiate from symptoms, allergic red eye from infective

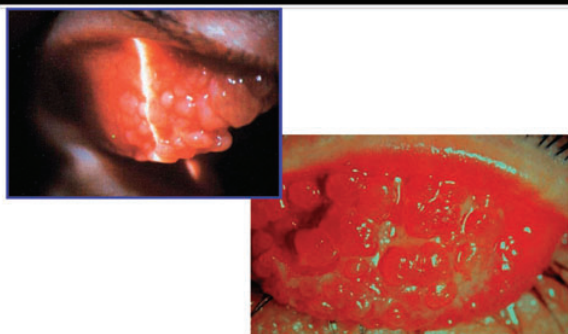
conjunctivitis related red eye. In SAC and PAC, itchiness is usually more prominent than grittiness and pain. Infective e.g. viral conjunctivitis patients usually have more pain. Tearing is usually less profuse in SAC and PAC than in infective red eye, the later is more likely to be associated with tears and discharge. History of known atopy/allergic rhinitis, history of contacts with persons with viral conjunctivitis, swab from inferior conjunctival cul-de-sac for culture, and conjunctival impression cytology are useful adjuncts.

Vernal keratoconjunctivitis

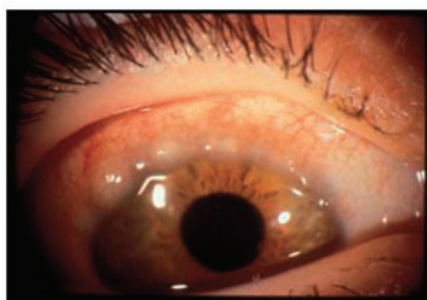
Vernal keratoconjunctivitis (VKC) is a rarer disease. It usually affects boys around age of puberty. According to a large case series in Italy,¹⁴ the average age of presentation of this disease is around 11 years old. The disease usually waxes and wanes over its course and its severity may stabilize towards the end of puberty. It is a clinically more severe and chronic disease and patients will suffer from flare ups over the years of the disease. Some of these patients also show a climacteric pattern, with spring and autumn being more common. Symptom-wise, these patients complain of itchiness, tearing, redness and ocular discharge which are different from acute allergic conjunctivitis in that they are more chronic. The clinical signs are helpful to distinguish VKC from SAC or PAC: include conjunctival injection, giant papillae in palpebral conjunctiva ("palpebral vernal"), Trantas' dots ("limbal vernal") and corneal complications such as punctate epitheliopathy and shield ulcers. Giant papillae are one of the hallmarks of the disease. They are papillary conjunctival mass of more than 1 mm in size on the tarsal conjunctiva. These are proliferation of collagen underneath the conjunctival epithelium. Its presence signifies prolonged chronic inflammation and conjunctival fibrosis can occur in the long term. The presence of giant papillae indicates poor prognosis of the disease. Trantas' dots are round gelatinous white elevations over superior limbal area. They are made up of collections of eosinophils. Corneal complications are secondary to the breakdown of corneal epithelium with subsequent plaque formation with fibrin and mucus deposits on the ocular surface. These will lead to delayed corneal healing and formation of shield ulcers. Shield ulcers only occur in 3-11% of VKC patients, but it can lead to permanent visual disability in 6% of all VKC cases.¹⁴



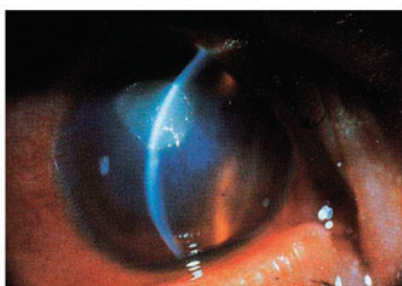
VKC – PALPEBRAL VERNAL



VKC – LIMBAL VERNAL



VKC – SHIELD ULCERS



Atopic keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is different from VKC in which the presentation is more chronic and signs and symptoms can continue into adult life. This is even rarer in incidence and is only seen infrequently by ophthalmologists. Essentially, patients suffer from the

different sequelae of chronic allergic inflammation. They can present with severe excoriation, pigmentation and scarring of the lids. The tarsal conjunctiva will no longer show giant papillae as in vernal keratoconjunctivitis but a featureless conjunctiva with scarring formation. The eye could be itchy and red at times but patients will start to have a less severe attack than before, partly because they are getting used to the disease. However they can present with dreadful complications on cornea which include microerosions and punctate epitheliopathy, macroerosions, shield ulcers and plaques forming on the macroerosions secondary to prolonged delayed healing of the corneal epithelium and deposition of calcium on the de-epithelialized cornea. They will also suffer from complications of cataract and even glaucoma. The cataract can be anterior subcapsular or posterior subcapsular in appearance. Some of these complication may be secondary to the diseases itself but also secondary to the prolonged use of topical steroids in vernal attacks.

VKC vs AKC– HOW TO DIFFERENTIATE^{a,b}

Characteristics	VKC	AKC
Age of onset	Younger age	Adults
Sex	M>F	M=F
Disease progress	More limited	Chronic
Seasonal variation	Spring	Perennial
Conj involvement	Upper tarsus; Large papillae	Lower tarsus; Smaller papillae
Conj scarring	Rare	Common
Trantas' dots	Common	Rare
Corneal vascularization	Rare	More common

a. Freisler KA et al: Allergic diseases of the lids, conjunctiva, and cornea. *Curr Opin Ophthalmol* 1997;8:25-30
b. Barney NP: Vernal and Atopic Keratoconjunctivitis. In *Cornea*. Mosby Year Book 1997, p 813

Comparison of Major Types of Allergic Conjunctivitis

	SAC	VKC	AKC	GPC
Corneal involvement	uncommon	common	common	uncommon
Exudate	watery	Thick, ropy	stringy	watery
Itching	moderate	intense	moderate	mild
Papillae	small	Large, flat-topped	small	Large, uniform in size & shape
Follicles	In chronic cases only	Yes	May develop in chronic cases	uncommon
Trantas' dots	none	common	common	uncommon
Conjunctival scrapings	Mast cells, eosinophils	Elevated IgE, mast cells, eosinophils	Mast cells, eosinophils, basophils, lymphocytes	Mast cells, eosinophils, basophils



Treatment modalities

The treatment for allergic conjunctivitis is multidisciplinary. Many of these patients may have associated atopic diseases such as asthma and rhinitis, which necessitates a multi-disciplinary approach involving paediatricians, medical physicians, general practitioners and clinical immunologists.

Avoidance of allergens is an important starting strategy. It is advisable to ask the children not to rub their eyes, since the act of rubbing will directly degranulate mast cells on ocular surface. Measures such as cold compression to peri-orbital areas, eyewashes with tear substitutes are also helpful ways to alleviate symptoms of allergic eye diseases. It is important to be aware that many of these patients are young and may not be able to tell a full clinical history.

For the ocular involvement, the mainstay of treatment includes topical medications. Oral medications are only indicated in very severe cases.

Current topical medications for allergic conjunctivitis included topical antihistamines, mast cells stabilizers, eosinophil deactivators and lubricants (Table 1). Anti-inflammatory drugs such as steroid and NSAID drops are usually required in more severe cases. The most common and useful medications with rapid relief of symptoms include antihistamines such as antazoline, levocabastine and emedastine. Through its immediate histamine receptor antagonism effect, these antihistamines can reduce itchiness, redness and swelling commonly seen in acute allergic blepharoconjunctivitis. The onset of action is also quicker than

the oral antihistamines. They can be used on a p.r.n. basis for those patients who have occasional allergic eye symptoms and can offer great relief. Oral histamine H₁-receptor antagonists such as astemizole, terfenadine and loratadine have also been shown to be effective in alleviating ocular symptoms. They are excellent choices when attempting to control multiple early-phase and some late-phase allergic symptoms in the eyes, nose and pharynx.^{13,15} But its clinical effect is offset by its longer time of action and accompanying systemic side effects such as sedation and dry mouth. Hence oral medications are not gaining popularity for treating allergic eye diseases.¹⁵ Recently, the newer second-generation antihistamines (cetirizine, fexofenadine, loratadine and desloratadine) are preferred alternatives over older first-generation antihistamines with fewer sedative and anticholinergic side effects.^{13,15}

Mast cells stabilizers are useful in the quiescent phase to prevent attack. The most commonly used medication is the sodium cromoglycate eye drops. The principle behind these mast cells stabilizers is that they can prevent mast cells getting degranulated and as a result the allergic and inflammatory cascade will not be initiated. Therefore it is especially useful if the patients can start the medications several days before the expected exposure of allergens. In cases of acute allergic attacks, its use in relieving symptoms may be less effective.^{8,15}

Topical vasoconstrictor agents provide rapid relief, especially for redness; however, the relief is often short-lived, and overuse of vasoconstrictors may lead to rebound hyperaemia and irritation.

Table 1. List of medications used in allergic conjunctivitis

Treatment modalities	Potential uses
Topical or oral antihistamine (antazoline, levocabastine and emedastine)	Symptoms relief
Topical mast cells stabilizer (sodium cromoglycate)	Prevention of attack
Topical combined agents (olopatadine, ketotifen)	Combined effects of antihistamines, mast cells stabilizers, eosinophil deactivators. Becoming the medication of choice in chronic allergies
Topical non-steroidal anti-inflammatory drugs (NSAID) (Ketorolac)	Effective in relieving symptoms, but less powerful than the combined agents
Topical steroids	Useful in severe attacks
Topical cyclosporine	Early evidence showed promising results, use in more severe chronic allergies



There are new agents with the combination of antihistamines, mast cells stabilizers, eosinophil deactivators in one medication. Recent data suggested superior clinical effects. Drops such as olopatidine (*trade name: patanol 0.1%*), ketotifen (*trade name: zaditen 0.025%*) and epinastine (*trade name: Elestat 0.05%*) may be superior in clinical response than the traditional antihistamines alone and therefore they now become the group of choice. The bd dosing regimen for most of these medications is also a potential benefit for these patients compared to some of the old antihistamines. Olopatidine is a selective histamine H1-receptor antagonist and has mast cells membrane stabilising properties, inhibiting the release of inflammatory lipid mediators such as leukotrienes and thromboxanes from polymorphonuclear leucocytes and eosinophils.^{16,17} Ketotifen is also a similar group of medication which blocks histamine1 (H1) receptors, stabilizes mast cells and inhibits chemotaxis and activation of eosinophils.^{18,19} Epinastine is another potent histamine H1 receptor antagonist which showed good in vivo and in vitro evidence in antiallergic and anti-inflammatory effects in addition to the antihistaminergic properties.²⁰ A randomized double-blinded control trial to look at the effect of olopatadine 0.1% versus placebo has shown a decrease in symptoms and signs score in seasonal allergic conjunctivitis with olopatadine.²¹ A double-masked environmental study on seasonal and perennial allergic conjunctivitis patients has revealed that olopatidine have overall better efficacy and comfort score than ketotifen.²² However, another randomized double-masked study comparing ketotifen and olopatidine showed no difference in clinical effects and improvement in inflammatory markers on conjunctival impression cytology.²³ Another recent randomized double-blinded placebo-controlled trial comparing the effect of topical olopatadine, ketotifen fumarate, epinastine, emedastine or fluorometholone acetate found that all medications except fluorometholone were equally effective in reducing itchiness and redness.²⁴ There were no clinical differences in terms of reducing tearing chemosis and swelling amongst the medications studied.²⁴ Compared to olopatadine, some studies have revealed that ketotifen and epinastine can have a higher degranulation inducing effects on corneal epithelial cells and mast cells. Therefore it may be less comfortable to use than the former.¹⁷ Further clinical trials are therefore necessary to look further into their side effects profiles and patient tolerability.

Non-steroidal anti-inflammatory drugs (NSAIDs), with its effect to inhibit prostaglandin synthesis including prostaglandins D2 and E2, have been seen with clinical effect on patients with seasonal allergic conjunctivitis. Ketorolac (*trade name: Acular 0.5%*) is one of the newer choice in this group that has been approved by FDA. Studies on ketorolac suggested a superior effect to control allergic symptoms than placebo.²⁵ A comparative study on ketorolac and olopatadine by Yaylali et al group (n=40) have revealed an equally effective profile in alleviating symptoms and signs of seasonal allergic conjunctivitis. However, olopatadine reduces ocular itching significantly more than ketorolac.²⁶ Therefore, topical NSAIDs are generally inferior for relief of allergic conjunctivitis when compared with olopatadine and emedastine.

Topical corticosteroids may be considered for more severe seasonal ocular allergy symptoms, although long-term use should be avoided because of risks of ocular adverse effects, including glaucoma and cataract formation.

Topical cyclosporine has gained a lot of interests in recent years. Treatment benefits were seen in patients with keratoconjunctivitis sicca (KCS) or chronic dry eyes (*trade name: Restasis 0.05%*)²⁷ and was successfully marketed after approval by the FDA in US. Evidence are now looming that this medication is also helpful in treating allergic eye diseases. Studies by Hingorani et al²⁸ and Akpek et al²⁹ have shown clinical improvement in both 2% and 0.05% concentration. However various studies have revealed conflicting results.²⁸⁻³² Its effective concentration and dosing regimen of this potential medication are yet to be worked out.

Previous studies revealed that topical cyclosporine could lead to a reduction of epithelial and stromal Class II MHC cells, T cells and IgA and IgG plasma cells in VKC patients, highlighting an immunomodulating effect on cell-mediated and humoral immune responses. The effect on mast cells and IgE mediated allergic responses are however not significant.³² Since VKC/AKC involves both IgE and non IgE mechanisms, cyclosporine should have some clinical effect on VKC. However, clinical effects and signs improvement need to be further quantified.

Patients with asthma and VKC could see some light in their treatment. Montelukast, a leukotriene receptor



antagonist has demonstrated its clinical effect in asthma patients. Its effect in controlling other atopic symptoms were further investigated.³³⁻³⁵ Early study by Lambiase et al.³³ on a group of 12 patients seemed to show significant improvement in physician-rated hyperemia, secretion, and chemosis as well as patient-rated burning, tearing, photophobia, secretion and redness in VKC patients. However, subsequent double blinded randomized trial on montelukast has not shown much clinical effect in ocular allergies.³⁵ At this stage, this medication does not seem to be a promising treatment in allergic conjunctivitis and further studies are warranted.

When instilling eyedrops and ointments, it is important to allow a rest of 3-5 minutes in between each application of different drops or ointment, in order to allow time for better drug absorption. It is usual to instill eyedrops before eye ointment, so that the ocular surface absorption of eyedrops will not be impeded by eye ointment. In applying eyedrops to children, it is not necessary to struggle with them by pulling open both eyelids for the application, nor it is necessary to apply the eyedrops directly onto eyeball, which can be frightening to them. The inferior eyelid, which is usually more lax than superior eyelid, can be gently pulled down to expose the inferior conjunctival cul-de-sac, and the eyedrops and ointment can be instilled effortlessly there even if the eyeball is completely under the superior eyelid. It is also a good idea to apply the medications while the child is asleep.

Pathways of communication are thought to increase the likelihood of an inflammatory reaction at both sites following allergen exposure of nasal or ocular tissue. Clinical trials of intranasal therapies have demonstrated efficacy in allergic conjunctivitis and rhinitis. Newer intranasal steroids decrease ocular symptoms, potentially achieving efficacy by suppressing the naso-ocular reflex, downregulation of inflammatory cell expression, or restoration of nasolacrimal duct patency. Proposed pathophysiologic interactions between allergic rhinitis and ocular allergy underscore the need for therapies with efficacy in both symptom sets.

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