

Topical treatment options for the management of allergic conjunctivitis

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Abstract

Allergic conjunctivitis (AC) is a common ocular condition that affects individuals of all ages but is particularly prevalent among those with atopic tendencies. It is a hypersensitivity reaction to environmental allergens such as pollen or animal dander. Ocular symptoms include itching (a hallmark symptom of AC), tearing, redness, and chemosis. While it is not a vision-threatening condition, AC can cause significant discomfort and impair quality of life. Management begins with allergen avoidance and non-pharmacological measures such as cold compresses and lubricating eye drops. First-line pharmacological treatment of seasonal and perennial AC typically involves topical antihistamines with mast cell stabilising properties which provide rapid symptom relief and long-term mast cell stabilisation.

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Introduction

Allergic conjunctivitis (AC) is an inflammatory condition of the conjunctiva (the clear membrane covering the white part of the eye and the inside of the eyelids) caused by an allergic reaction to allergens such as pollen, dust mites or animal dander. It is often associated with other atopic diseases such as asthma or allergic rhinitis.¹⁻⁵

Ocular allergy affects at least 20% to 40% of the world’s population annually, with incidence rates increasing.^{1,2} It mostly starts in young adults, with onset around 20 years of age.² The prevalence and symptoms tend to decrease with age.^{1,2} However, AC can also occur for the first time in older adults, but this is not typical.²

Seasonal and perennial forms of AC typically do not pose a threat to vision. However, AC can cause substantial suffering and has a negative impact on the patient’s quality of life.¹⁻³

The allergic cascade

The ocular mucosa has a large surface area, which is highly accessible to allergens.⁴ AC is a classic type I immunoglobulin E (IgE) mediated hypersensitivity reaction.² The different phases involved in ocular allergy are described in Table I.

Signs and symptoms

Usually both eyes are affected, but sometimes one eye can be affected more than the other.² Allergic conjunctivitis typically does not pose a threat to vision. Signs and symptoms include:¹⁻⁴

- Pruritus (hallmark sign)
- Redness
- Tearing/discharge (typically watery and nonpurulent [clear])
- Chemosis (swelling of the conjunctiva)
- Blurred vision
- Burning
- Mild crusting upon awakening
- Mild photophobia

AC is commonly associated with other atopic conditions such as allergic rhinitis, asthma and atopic dermatitis.^{1,4} Therefore, other symptoms may also be present.²

Types of AC

AC can be divided into acute, seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC).^{1,2,4,6} Key differences are listed in Table II.

Table I: Summary of the sensitisation, early and late phases of ocular allergy^{1,2,4}

Phase	Timing/duration	Notes
Step 1 Sensitisation	Initial exposure to allergen	• Initial exposure to allergens triggers production of allergen-specific IgE, which binds to mast cells in the conjunctiva
Step 2 Early Phase (Immediate response)	Starts within seconds to minutes after re-exposure to the allergen Lasts for 20–30 minutes ⁴	• The allergic cascade is initiated when an allergen comes into contact with the ocular surface in a sensitised individual (a person who is allergic to that specific allergen) • The binding of IgE to sensitised mast cells, leads to mast cell degranulation and the subsequent release of inflammatory modulators such as histamine, tryptase, leukotrienes and prostaglandins
Step 3 Late phase	Starts about 6–10 hours after the initial allergen exposure	• Characterised by the influx of other inflammatory cells such as eosinophils, basophils and neutrophils, followed by lymphocytes and monocytes • This leads to continuous inflammation, persistent symptoms and consequently an increased likelihood of tissue damage

Table II: Key differences between acute, seasonal and perennial AC^{1,2,4,6}

	Causes	Notes
Acute AC	Environmental exposure, typically to a known allergen, such as cat dander	- Sudden-onset - Symptoms can develop as quickly as 30 minutes after exposure - Characterised by intense episodes of itching, tearing, chemosis, hyperaemia - Self-limiting, symptoms usually resolve within 24 hours once exposure to allergen has ended
SAC	Exposure to outdoor airborne pollens, e.g. tree, grass and weed pollens (depending on the season and geographical location)	- Onset is usually less dramatic and more gradual; develops over days to weeks - Course is predictable and corresponds to one or more specific pollen season(s) - Commonly associated with allergic rhinitis
PAC	Environmental exposure to year-round, usually indoor allergens, e.g. animal dander, mould spores and dust mites	- Present throughout the year (chronic) - Symptoms are usually mild, and fluctuate (waxing and waning)

Table III: Main characteristics of VKC and AKC¹⁻⁴

Type	Demographics and/or associations	Signs and symptoms
VKC	More common in males (3–25 years of age) living in warm, dry, subtropical climates May vary with seasons	Intense ocular itching Stringy mucoid discharge Large cobblestone papillae on the upper tarsal conjunctiva Corneal ulcer (shield) may form in severe cases
AKC	More common in males (30–50 years of age) Associated with a history of atopic dermatitis and eczema	Chronic and severe disorder that can affect the eyelid, conjunctiva, and cornea Severe itching (with seasonal variability) Corneal scarring, neovascularisation Eyelids may become thickened and lichenified

More severe forms of AC

SAC and PAC are the two most common and milder forms of ocular allergic disease.^{3,4} However, corneal involvement in the more severe forms of allergic eye diseases such as vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) can potentially affect vision, if left untreated (Table III).^{1,3,4,7}

Allergic conjunctivitis or infection?

Table IV highlights the key differences between viral, bacterial and AC.

Concomitant conditions

More than one condition can co-exist in the same patient.² For example, dry eye and AC can co-exist, and each condition can

worsen the other.⁶ Reasons for this include a higher concentration of allergens on the surface of the eye due to tear film insufficiency and/or reduced ability to rinse away foreign substances such as allergens.⁶

Treatment

Management of AC typically begins with allergen avoidance and non-pharmacological measures such as cold compresses and artificial tear drops (Table V). Table VI contains a list of topical therapies used for the management of AC, with the focus on SAC and PAC.

Non-pharmacological

The first step in managing SAC and PAC is to implement preventative measures to avoid or reduce exposure to known

Table IV: Differential diagnosis between viral, bacterial and allergic conjunctivitis^{1-4,8}

	Allergic	Bacterial	Viral
Itching	Itchiness is a characteristic symptom and the main complaint	Usually, no itching	Usually, no itching
Ocular discharge	Watery, or stringy discharge	Purulent discharge Usually white but may be green or yellow Mucopurulent secretions with bilateral glued eyes upon awakening	Clear and watery Profuse tearing
Unilateral/ bilateral involvement	Usually, bilateral (sometimes one eye is more affected than the other)	Usually, unilateral, but may spread to the other eye	Initially unilateral, but spreads to the other eye within a day or two
Appearance of eyelid oedema	Redness in both eyes with swelling of eyelids	Moderate	Minimal
Other symptoms	Commonly associated with other atopic conditions such as allergic rhinitis, eczema or asthma	Foreign body sensation Mild pain in the eye(s)	Symptoms such as fever, sore throat, and/or malaise may be associated with adenovirus infection

Table V: Examples of topical artificial tears¹¹⁻¹⁶

Preservative-free single dose units (SDU) or unit doses (UD)	Preservative-free formulations	Preservative-free in eye	Preservative included
Artelac® Splash SDU Artelac® Advanced SDU Artelac® Moisture SDU Optive® Plus UD Optive® Fusion™ UD Xailin® Fresh SDU	Artelac® Splash (10 ml has UNIQUE applicator) Xailin® Night (Ointment) Xailin® Plus 0,2% HA	Artelac Intense® Rebalance (10 ml contains Oxyd®) Optive eye drops (10 ml contains PURITE®) Xailin® Hydrate (contains stabilised oxychloro complex [SOC])	Artelac® Moisture (10 ml contains cetrimide) Xailin® Gel (contains cetrimide) Tears Naturale® II (15 ml contains polyquaternium)

allergens. However, this is often challenging since many allergens are airborne, making it difficult to completely prevent contact with the ocular surface.^{1,6}

Other non-pharmacological measures include:^{1,6}

- Using a cool compress. This may help to reduce eyelid, periorbital oedema and discomfort.
- Avoid or reduce contact lens wear during the symptomatic periods (if applicable). The reason for this is that allergens can adhere to contact lens surfaces.

Note: Avoid rubbing the eyes. Rubbing may cause mechanical mast cell degranulation, thereby worsening allergy symptoms.^{1,6}

Artificial tears

Refrigerated artificial tears may be used frequently, throughout the day.^{1,6} In addition to providing a cooling and soothing effect, artificial tears also help to dilute and flush allergens from the eye(s).⁶

Patients with mild symptoms, as well as those with both allergic conjunctivitis and dry eye generally respond well to frequent use of artificial tears or lubricating gels (2–4 times daily).^{1,5,6,9} Artificial tear drops are usually used during the day, while more viscous products and ointments are usually preferred at bedtime as they may cause transient blurring of vision.^{9,10}

Artificial tear formulations are designed to restore and maintain tear film stability while protecting the ocular surface (examples listed in Table V). Artificial tears may contain one of the following main ingredients or a combination thereof:⁹⁻¹¹

- Lubricants (e.g. carbomers, cellulose derivatives, hyaluronic acid or povidone) increase the tear film viscosity and reduce evaporation.
- Lipid-based agents and surfactants (i.e. lanolin, castor oil or paraffins), serve to replenish the deficient lipid layer of the tear film, thereby minimising evaporation.
- Electrolytes (e.g. sodium, potassium, and chloride) are sometimes included to maintain ocular surface homeostasis and to help stabilise tear film osmolarity.
- Osmo-protectants (e.g. betaine and glycerine) protect cells from hyperosmotic stress and dehydration.

Preservatives such as benzalkonium chloride are toxic to the corneal epithelium and can cause harm, particularly with frequent

use. A preservative-free formulation may be more suitable for patients who need to use artificial tears frequently as well as for those with sensitive eyes.^{5,9,11,12}

Vanishing types of preservatives (e.g. stabilised oxychloro complex [SOC]) disappear upon contact with the eye. These preservatives are converted into water, oxygen, sodium and chloride.¹⁰ These products are sometimes labelled as “preservative-free in eye”.¹³

Microbial filters or membranes with antimicrobial properties are used in some of the multidose vials to maintain the sterility in the multidose vial. The use of these filters or membranes is emerging as an alternative to the use of preservatives.¹⁰

When to refer

Patients presenting with eye trauma, chemical agent exposure, visual loss, any visual impairment or photophobia should be referred to an ophthalmologist, for urgent evaluation and treatment.⁸

In addition, referral to an ophthalmologist is recommended for patients:

- Presenting with ocular pain. Ocular pain is not commonly reported in AC.^{1,2}
- With AC who do not respond to two or three weeks of consistent therapy with an antihistamine with mast cell-stabilising properties.⁶
- With co-existing allergic rhinitis and/or asthma that are not well controlled.⁶

From a practical point of view

Avoid repetitive blinking

After the drop has been instilled, repetitive blinking should be avoided. Repetitive blinking generates a negative pressure in the eye and could cause topical medication to wash out more quickly, thus reducing the contact time and absorption into ocular surfaces.⁶

When using multiple eye drops, for example a topical medication and artificial tears

It is advisable to instil the first drop and then wait a few minutes (3–5 minutes) before instilling the second drop. This is to avoid diluting the first drop and/or to ensure that the instillation of a second drop does not wash out the first.⁶

Table VI: Summary of topical therapies for the management of AC^{1,3,6-8,12,14,17}

	Action	Examples	Notes	When to consider	Potential ocular side-effects
Antihistamines with mast cell-stabilising properties (dual-acting)	Block histamine receptors Prevent degranulation of mast cells and inhibit the release of proinflammatory mediators from mast cells (limit the release of histamine, tryptase and prostaglandin D2) Also inhibit leukocyte activity and inhibit mediator release from eosinophils, basophils and neutrophils	Olopatadine (Patanol [®] , Olopaten [®] , Olopaten [®] Once daily)	Decrease histamine levels in the tear film, resulting in an improvement of itching, tearing and chemosis, even with continued use	Often used as first-line treatment for SAC and PAC A more suitable option than vasoconstrictor-containing products for those who have frequent attacks (more than two days per month)	Burning and stinging upon installation Increased ocular dryness
		Azelastine (Optilast [®])	Address both the immediate (acute) symptoms and the chronic aspects of AC		
		Epinastine (Relestat [®])	A quick onset of action and due to their ability to prevent further release of inflammatory mediators and to stop the recruitment of inflammatory cells, they have a longer duration of action compared to single acting antihistamines		
		Ketotifen (Ketagex [®])			
Ocular decongestants	Activate the postjunctional, alpha-adrenergic receptors found in blood vessels leading to vasoconstriction and decreased conjunctival oedema	Naphazoline (Safyr Bleu [®] , Oculosan [®])	Provide symptomatic relief Cause decongestion and whitening of the eye	Episodic treatment (< 2 weeks at a time) of ocular redness associated with minor eye irritation	Slight transient local stinging Regular, extended use (for longer than 2 weeks) can lead to rebound conjunctival hyperaemia (rebound redness) and tachyphylaxis (reduced effectiveness) Chronic use can lead to conjunctivitis medicamentosa
		Oxymetazoline (Oxylin [®] , Allergex [®] eye drops)	Does not treat the cause of the symptoms Have little effect on itching		
		Tetryzoline (tetrahydrozoline hydrochloride) (see decongestant/antihistamine combination)	Not suitable as a standalone treatment for AC		
Topical antihistamines	H1 receptor antagonists reversibly bind to histamine receptors on the conjunctiva and eyelids	Emedastine (Emadine [®]) Levocarbastine (Livostin ED [®]) Antazoline (see decongestant/antihistamine combination)	Second generation topical antihistamines (e.g. emedastine, levocabastine) have a longer duration of action compared to first-generation antihistamines (e.g. antazoline)	For the relief of signs and symptoms associated with the release of histamine, such as itching, tearing and oedema	Dryness and irritation
Decongestant/antihistamine combinations	Refer to single agents	Tetryzoline/antazoline combination eye drops (Spersallerg [®] , Gemini [®])	Vasoconstrictor/antihistamine combination usually works better compared to single-agent topical products, for example, vasoconstrictors or antihistamines only	Suitable for episodic or short-term relief of symptoms	As for single agents Use < 2 weeks to prevent rebound conjunctival hyperaemia
Mast cell stabilisers	Inhibit degranulation of mast cells, thereby reducing the release of allergic mediators from mast cells	Sodium cromoglycate (cromolyn sodium) (Stop-Allerg [®]) Lodoxamide (Alomide [®])	Act before the mast cell is degranulated. As a result, are not effective for the management of existing acute symptoms once inflammatory mediators have already been released Efficacy is only reached 5–14 days after treatment has been initiated	Prophylactic option for people with SAC who cannot use other topical treatments Treatment should be started two to four weeks before the pollen season starts	Burning and stinging
Corticosteroids	Inhibit phospholipase A and the synthesis of lipid-derived mediators (prostaglandin and leukotriene) from arachidonic acid	"Soft" corticosteroids: Loteprednol (Lotemax [®]), Fluorometholone (FML Liquifilm [®])	"Soft" corticosteroids are designed to quickly inactivate upon penetration of the cornea, which reduces their risk of increasing intraocular pressure	Topical "soft" corticosteroids are reserved for short-term (no longer than two weeks) treatment of severe or refractory cases when antihistamines with mast-cell stabilising properties have not provided adequate symptom relief, or to control acute exacerbations	Elevated intraocular pressure (IOP), glaucoma, cataract formation, secondary infections and delayed wound healing
		Ketone-based topical steroids: Dexamethasone phosphate (0.1%) (Maxidex [®] , Spersadex [®])	Potent ketone-based topical steroids carry a higher risk of ocular side-effects and of increasing IOP	Treatment needs to be initiated by an ophthalmologist and careful monitoring is required	
		Prednisolone acetate 1% (Pred Forte [®])			

Table VI: Continued

	Action	Examples	Notes	When to consider	Potential ocular side-effects
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Act on the inflammatory pathway by blocking the cyclooxygenase Inhibit the conversion of arachidonic acid to prostaglandins and thromboxanes	Ketorolac tromethamine (Acular [®] , Kelopt [®]) Diclofenac (Voltaren Ophtha [®] SDU) Nepafenac (Nevanac [®] , Ilevro [®])	Mainly used for the treatment of perioperative inflammation in cataract surgery	Due to potential side-effects, the use of topical NSAIDs for acute AC should be limited to short-term use, as an add-on therapy, in patients whose symptoms are inadequately controlled with antihistamines with mast cell stabilising properties	Risk of corneal melting (corneal epithelial breakdown), a severe side-effect that can lead to sight-threatening corneal side-effects (keratitis, ulceration or perforation), particularly in individuals with pre-existing ocular surface disease
Topical immune-modulators	Inhibit T-cell activation	Cyclosporin Tacrolimus	Steroid-sparing therapeutic alternatives	Considered under specialist supervision for the management of patients with more severe allergic eye disease and for patients with persistent flare up of their AC	Burning, irritation

Contact lens wearers

Contact lens wearers should refer to the prescribing information for guidance before using eye drops.¹²

Reducing systemic side-effects

Absorption of topical agents into the circulation may lead to systemic side-effects.¹² Drugs may enter the circulation directly from the capillaries present in the conjunctiva, but to a greater extent from the nasal mucosa, which receives drainage from the eye's tear ducts, or even from the stomach via the back of the throat after being swallowed.¹² The risk of systemic side-effects may be minimised by:

- Applying pressure on the lacrimal sac for 1–2 minutes after instilling the drop or
- Closing the eye after instilling the drop, this also increases the contact time with the cornea, leading to better absorption of the drug into ocular tissues.^{6,12}

Safety considerations listed in this article are not all-inclusive. Please refer to the relevant package insert for additional information regarding dosing, side-effects, special precautions, contraindications, and monitoring instructions.

Conclusion

Despite its high prevalence, AC is often self-managed leading to suboptimal treatment, underdiagnosis, and potential complications. While not vision-threatening, SAC and PAC can substantially affect quality of life. Management involves allergen avoidance, non-pharmacological measures, lubricating eye drops as well as topical antihistamines and dual-action agents (first-line treatment option).

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