Beat the itch: allergic conjunctivitis and its management

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Abstract

Allergic conjunctivitis (AC) includes a range of conditions triggered by allergens found in the environment, and specifically affecting the eyes. Because patients do not seek medical assistance, and most prefer to treat with over-the-counter medicines, accurate diagnosis is often not possible. AC typically does not impair vision; however, the symptoms can diminish quality of life. Early diagnosis and proper treatment are crucial to enhance patients' quality of life, reduce recurrence rates, and prevent potential complications. AC typically affects both eyes and is characterised by common symptoms and signs such as itching, sensation of having a foreign body in the eye, watery or mucus-like discharge, redness of the conjunctiva, and reaction involving papillae on the inner surface of the eyelid. The primary goal of non-pharmacological management is the avoidance of allergens. Pharmacological management includes the administration of topical antihistamines, vasoconstrictors, mast-cell stabilisers and anti-inflammatory agents. The correct way of administering the eye drops to the eye is important, and the pharmacist may play a crucial role in educating patients.

Keywords: allergic conjunctivitis, management, eyes

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Introduction

Allergic conjunctivitis (AC) comprises a range of conditions triggered by the eyes' reaction to allergens found in the environment, impacting as much as 40% of the world's population.[1,2] Despite being widespread, a significant number of those affected fail to seek medical assistance, resulting in inadequate diagnosis and treatment.[2] There are recognised connections between allergic rhinoconjunctivitis and other allergic conditions such as asthma, eczema, food allergies, and eosinophilic esophagitis.[3] Most patients experience concurrent allergic rhinitis, with only 6% having symptoms limited to the eyes.[3] Approximately 44% of children and 20% of adults diagnosed with asthma display symptoms indicative of AC.[3] This underscores the significance of gathering specific details about ocular symptoms when evaluating patients to accurately assess their eye involvement.[3] While AC typically does not impair vision, it presents significant symptoms and substantially diminishes the quality of life for affected individuals, particularly children and adolescents who are more prone to certain types of the condition.[1] In some cases, severe forms of AC can adversely affect vision by complicating and potentially leading to corneal scarring and pannus formation (growth of fine blood vessels onto the clear corneal surface).[1] Therefore, early diagnosis and proper treatment are crucial to enhance patients' quality of life, reduce recurrence rates, and prevent potential complications.[1] AC typically affects both eyes and is characterised by common symptoms and signs such as itching, sensation of having a foreign body in the eye, watery or mucus-like discharge, redness of the conjunctiva, and reaction involving papillae on the inner surface of the eyelid.[1]

Aetiology

The types of AC include acute, seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), Vernal Keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary reaction (GPC).[1,4] However, the most common types of AC are SAC and PAC, which account for over 95% of ocular allergy cases in the United States.[1] The allergens that are attributed to SAC are tree pollen, wood pollen and grass pollen, with grass pollen representing the most frequent allergen.[4,5] Dust mites or pet hair, animal dander and moulds are the primary sensitisers in PAC. Ocular symptoms can sometimes be caused by food allergens as well.[4,5]

Pathophysiology

The cornea and conjunctiva provide barrier protection for the eye, against foreign invasion of environmental elements.[6] The ocular mucosa has a large surface area, which exhibits different immunological responses, which result in the inflammation of the cornea and conjunctivitis. AC is a type 1 immunoglobulin-E (IgE) mediated hypersensitivity reaction.[7] The direct contact between an allergen and the ocular surface triggers the allergic reaction. Type 2 helper T (Th2) cells, in sensitised individuals release pro-inflammatory cytokines (IL-3, IL-4, IL-5 and IL-13), which stimulate the production of IgE by the B-cells (a type of immune system blood cell).[3] IgE binds to mast cells, resulting in mast cell degranulation. Inflammatory modulators such as histamine, tryptase, leukotrienes and prostaglandins are subsequently released.[6]

The activation of the allergic cascade occurs within seconds to minutes after exposure to an allergen and this early phase clinically lasts for 20-30 minutes.[8] The symptoms experienced in the early phase include pruritus, chemosis, redness and watering

of the eyes. The late phase of the allergic response begins a few hours after initial exposure. It is characterised by increased vascular permeability, migration of inflammatory cells such as the eosinophils, lymphocytes and neutrophils.[2] Furthermore, the inflammation continues, symptoms persist, and this results in tissue damage.[2]

Non-pharmacological treatment measures

Allergen avoidance is a primary goal in the management of all types of AC. However, this routine recommendation may be impossible to avoid in the presence of airborne allergens due to the large surface area of the eyes. The exposure to pollen and outdoor mould can be decreased by closing windows and use of air conditioners.[3] Frequent cleaning of households and using air filters will provide relief from environmental allergens, such as house dust mites and pet dander. Patient awareness to avoid outdoor activities during seasons with high allergens, should be increased to reduce exposure to allergens. Wearing masks for additional protection may also reduce exposure to allergens. Cold compresses provide relief from inflammation and alleviate ocular symptoms such as itching. Wearing wraparound glasses improves photophobia and can decrease contact with airborne allergens.[9]

Pharmacological treatment

One third of patients with AC are normally undiagnosed and untreated.[1] The majority of patients with ocular allergic disease prefer self-medication with over-the-counter (OTC) preparations, regardless of their ability to lose effectiveness overtime with prolonged use.[5] Common adverse effects resulting from overuse of OTC therapies, include ocular toxicity, which is induced by the preservative benzalkonium chloride (BAK), used in about 70% of OTC eye drops, rebound vasodilation, and tachyphylaxis.[4,10] Anti-allergic eye drops that maintain ocular surface homeostasis while avoiding the toxic effects of preservatives such as topical antihistamine bilastine and dual agents olapatadine, ketotifen, and azelastine should be considered as standard of care.[5]

In recent practice, the use of vasoconstrictors and decongestants, antihistamines, mast cell stabilisers, topical corticosteroids, NSAIDs, and dual-acting agents as treatment options are mainly aimed at relieving and controlling symptoms.[6] The types of treatment options available for AC are listed in Figure 1. However, there's been significant advances in the treatment of severe or ocular allergy, particularly in immunomodulators and immunotherapy, which are the only disease-modifying treatments available and may provide lasting benefit.[11]

The choice of treatment for AC is dependent on the presence of signs and symptoms on diagnosis, the identification of signs of multisystem disease as in generalised allergic symptoms and in cases of failure of current therapy to control symptoms.[3] As such a treatment algorithm is used in the management of newly diagnosed patients and patients with long standing AC**.** The following treatment algorithms were derived from clinical trial studies and systematic reviews together with specialist advice in clinical practice. They provide an overview on the stepwise approach taken towards the treatment of AC.[3]

Topical treatment

Vasoconstrictors and decongestants

Naphazoline is among the first FDA approved α-adrenergic agonists used as OTC agents in 1971, followed by other agents such as tetrahydrozoline, phenylephrine, ephedrine, and brimonidine.[1] The mechanism in AC through sympathomimetic vasoconstriction decreases congestion at the site of administration and provides symptomatic relief for eye redness and itching.[12] Alpha-adrenergic agonists have a rapid onset but short duration of action. They are commonly known for causing tachyphylaxis, rebound hyperaemia, mydriasis, and blepharitis, and are not recommended in adolescents and children.[1] Their effectiveness as decongestants has only been proven when used together with topical antihistamines in clinical trials.[12]

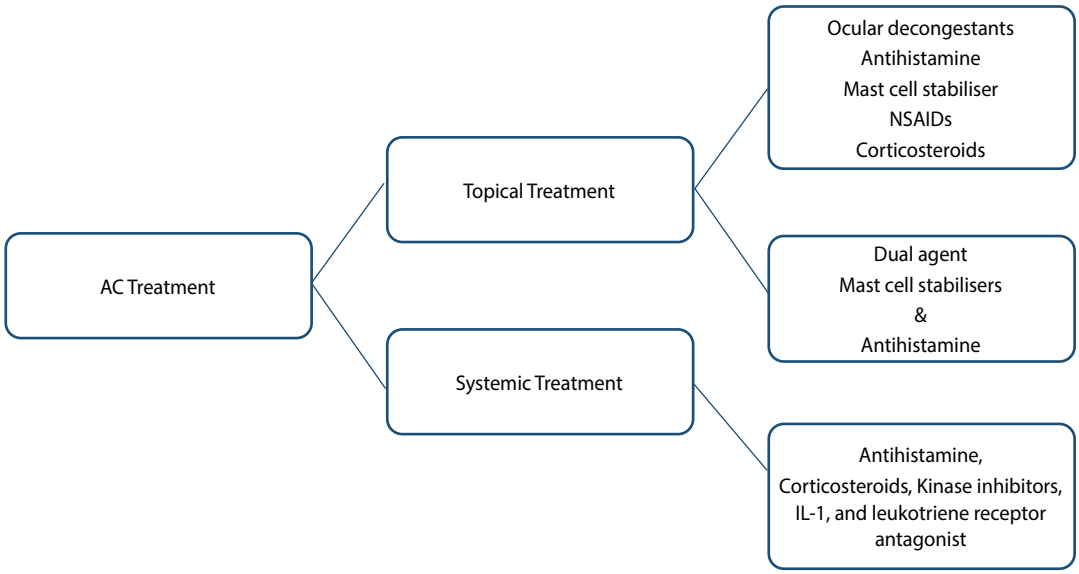

Figure 1: Pharmacological treatment used for allergic conjunctivitis[3]

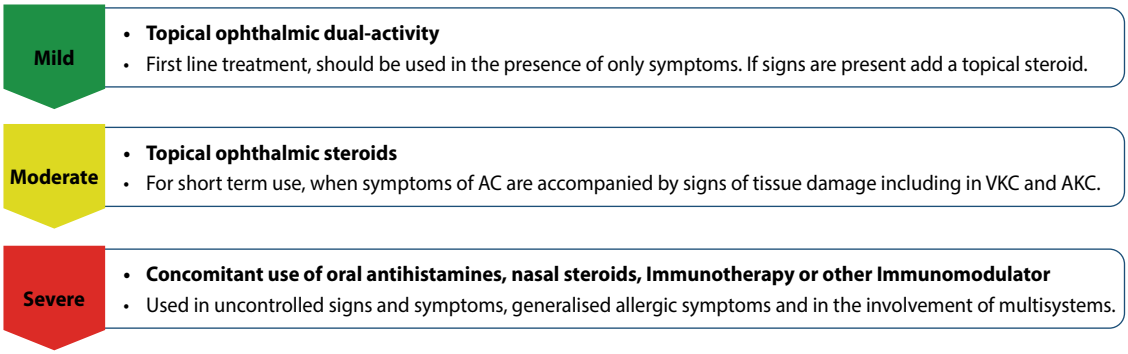

Figure 2: Illustrates the Treatment Algorithm for AC[3]

Antihistamine

Topical antihistamine agents exert their action by blocking H1-receptors thus preventing histamine binding and activity at the H1 receptor site. They are indicated for symptomatic relief of itching, redness and teary eyes.[13] Antazoline and pheniramine are examples of first-generation topical antihistamines that were used for AC, however, they are poorly tolerated and have a limited potency and short duration of effects. These are often combined with the vasoconstrictors naphazoline and tetrahydrozoline, (Spersallerg), to increase half-life and reduce dosing frequency, but have been recently replaced by newer agents like levocabastine and emedastine.[12] Possible side effects include eye sting, sedation as they cross the blood-brain barrier and keratitis.[14]

Mast cell stabilisers

Mast cell stabilisers are used as prophylactic therapy. They inhibit mast cell degranulation and the release of histamine by preventing calcium influx across mast-cell membranes.[15] Common examples of mast cell stabilisers include cromolyn sodium, lodoxamide and pemirolast. Lodoxamide is mostly preferred over cromolyn sodium, as it has a more rapid onset of action with less stinging.[16] The concurrent use of mast cell stabilisers with topical steroids or H1-antagonists for the first few weeks of therapy is advised due to delayed time to reach peak efficacy and not having immediate relief from symptoms.[16]

Topical corticosteroids

Topical ophthalmic corticosteroids (loteprednol [0.2%, 0.5%, fluorometholone alcohol 0.1%) are indicated in severe ocular allergy and in acute exacerbations as short, pulsed therapy.[12] They cause inhibition of phospholipase A, resulting in inhibition of prostaglandins and leukotriene synthesis.[1] Though these agents are highly effective, they may cause severe adverse reactions such as increased intraocular pressure, increased susceptibility to infections, cataract development, and delayed wound healing.[5]

Table I: Characteristics of topical agents used for the treatment of SAC and PAC

Topical agent	Example of the drug	Dose	Dosing frequency
Antihistamines	Cetirizine	2.4 mg/ml	Three times daily
	Levocabastine	0.5 mg/ml	Twice daily
	Bilastine	0.6 mg/ml	Once daily
	Emedastine	0.5 mg/ml	Twice daily
Corticosteroids	Antazoline + tetryzoline (Spersallerg)	0.5 mg/ml, 0.4 mg/ml	Three to four times per day
	Dexamethasone 0.01%	1 mg/ml	Four to 6 times daily
	Loteprednol (0.2%, 0.5%)	5 mg/ml	Four times daily
	Fluorometholone alcohol 0.1%	1 ml/mg	Two to four times daily
Mast Cell S tabilisers	Cromolyn sodium		Four to six times daily
	Lodoxamide	1 mg/ml	Four times daily
	Pemirolast	1 mg/ml	Four times daily
NSAIDs	Ketorolac	5 mg/1ml	Four times daily
	Nepafenac	1 mg/ml	Three times daily
		4 mg/ml	
	Bromfenac	0.9 mg/1 ml	Twice daily
Dual-action agents	Ketotifen	0.025 mg/ml	Twice daily
		0.05 mg/ml	
	Olopatadine	1 mg/ml	Twice daily
		2.22 mg/ml	Once daily
	Epinastine	0.5 mg/ml	Twice daily
	Bepotastine besilate	15 mg/ml	Twice daily
	Alcaftadine	2.5 mg/ml	Twice daily
	Azelastine	0.5 mg/ml	Twice daily

Intranasal steroids such as fluticasone furoate, and mometasone furoate have also been considered in the management of AC to reduce ocular symptoms associated with allergic rhinitis.[12]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs inhibit the cyclooxygenase pathway and thus reduce the synthesis of prostaglandins and thromboxane.[11] They are indicated for short term relief of pain. However, they cause a myriad of side effects such as stinging, keratitis, ocular hypertension and are contraindicated in patients with asthma and nasal polyps.[1] Examples of topical NSAIDs include ketorolac 0.4%, nepafenac, and bromfenac.

Dual-acting agents

Topical dual-acting agents have both local antihistamine and mast cell stabilising properties. They are preferred as first-line agents by allergists and eye practitioners in the management of AC.[1] They are clinically superior monotherapy agents as they provide both prophylactic benefit and immediate symptom relief.[17] Ketotifen, olopatadine, alcaftadine, and bepotastine besilate are examples of the most used topical dual agents. Olopatadine was the first dual agent approved by the FDA in 1996.[1] It has been found superior to other agents in reducing itching and redness, decreasing the tear histamine level, decreasing chemosis, eyelid oedema and significantly improving quality of life.[3,18]

Table I highlights the examples of the topical ophthalmic preparations, and further outlines the dosing regimen, and the frequency of administration of each drug.

Systemic treatment

Systemic treatment for AC includes systemic antihistamines (cetirizine, loratadine), corticosteroids (prednisolone), selective glucocorticoid receptor agonists (SEGRAs), kinase inhibitors, IL-1 receptor antagonist, and leukotriene receptor antagonist. Systemic antihistamines are less effective in treating AC but have been deemed effective in patients with comorbid rhinitis or sinusitis.[19] SEGRAs are targeting the anti-inflammatory pathway of corticosteroids to cause effect with less side effects. Kinase inhibitors, IL-1 antagonists and leukotriene receptor antagonists play their role in the inflammatory cascade at a molecular level.[1]

Immunomodulators

The two immunomodulators topical calcineurin inhibitors cyclosporine A (CsA) and tacrolimus are used in the treatment of GPC, VKC and AKC. Recent studies have shown tacrolimus to be the same if not more effective than CsA in the management of VKC and is used in patients not responding to CsA.[8] In cases of severe AC such as AKC and VKC, systemic immunosuppression with CsA, tacrolimus or mycophenolate mofetil is achieved. The side effects of treatment with calcineurin inhibitors include stinging/burning sensation, and the risk of molluscum contagiosum virus, papillomavirus, or herpesvirus infection.[12]

Immunotherapy

Immunotherapy provides etiological treatment and should be administered under the guidance of a specialist.[5] The main objective of immunotherapy is to reduce the occurrence and prevent the recurrence of symptoms when exposed to known allergens.[1] Immunologic changes that take place include the downregulation of T2 response and upregulation of regulatory T cells that produce inhibitory cytokines, resulting in a less end-organ response to allergen exposure.[3] Two main types of immunotherapies include sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT).[3]

Patient education for topical medicine administration

In most patients, eye-drop administration errors increase the risk of treatment failure or harmful adverse effects.[20,21] Beyond compliance, the eye drop administration technique consists of

Figure 3: Application of ophthalmic solutions or suspensions[24]

numerous action steps, which can variably affect the efficacy of the medicine.[22] Most patients fail to instil eye drops correctly, which include positioning of the dropper bottle, the force required to produce a drop from the bottle or trying to avoid accidental contamination of the dropper.[22] Contamination during handling by the end user is a risk for microbial transmission and infections.[23] Patient education is a promising approach to prevent mistakes in eye drop administration, and the pharmacist can play a crucial role in providing education to patients.[22] Refer to Figure 3 for the application of eye drops.[24]

Conclusion

AC is one of the most common ophthalmic conditions, however, it remains as one of the most undiagnosed and undertreated conditions. The vast options of OTC medications available for symptomatic relief have led to many patients opting for self-medication rather than seeking medical advice. This has resulted in patients being treated with AC at an advanced stage where medical therapy is ineffective or has progressively led to ocular damage. Treatment options available for AC include topical agents administered for symptomatic relief and systemic agents normally given in patients with comorbid rhinitis or sinusitis. The development of immunomodulators and immunotherapy agents aims at reducing the occurrence and recurrence of AC through etiological management. Patient education on administration techniques plays a huge role in ensuring treatment efficacy, thus should be a key area of note in managing patients with AC.

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