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ALLERGIC CONJUNCTIVITIS: TREATMENT UPDATES AND LONG-TERM MONITORING

Introduction

Allergic conjunctival diseases have a significant impact on the ocular surface, affecting the conjunctiva, cornea, and eyelids. Estimates indicate that approximately 35% of North Americans are affected by these diseases.[1-5] Seasonal and perennial allergic conjunctivitis are the most common and mildest forms of ocular allergic disease, affecting 15–20% of the population.[4] lMore severe conditions of ocular allergenic diseases include atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis (GPC). This article will review allergic conjunctivitis classifications, ocular sequelae, and a simplified treatment algorithm.

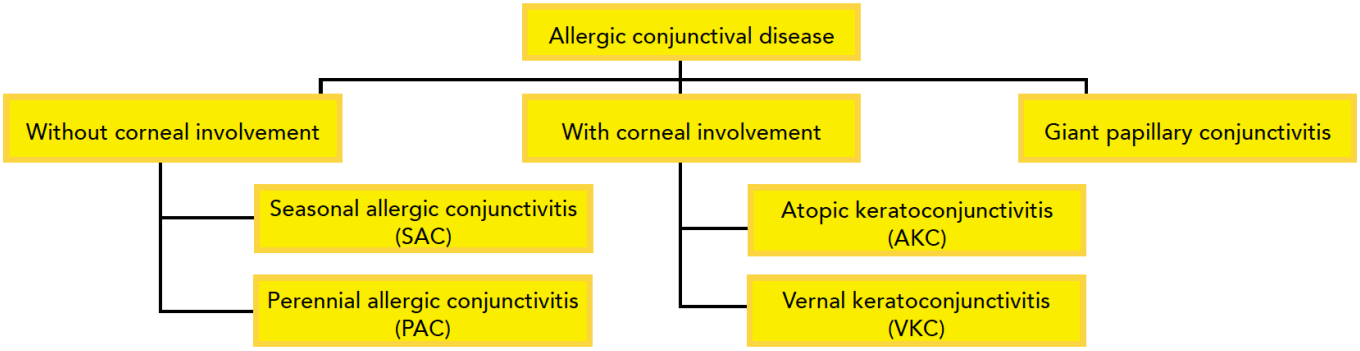

Figure 1. *Top Classification of allergic conjunctival diseases; courtesy of Clara C. Chan, MD and Caberry Yu, MD*

Classification

Seasonal allergic conjunctivitis (SAC), also known as hay fever conjunctivitis, is triggered by allergens from trees, grass, pollen, and weeds. Patients commonly have comorbid conditions such as asthma and allergic rhinitis.[5] Perennial allergic conjunctivitis (PAC) persists year-round, with animal dander, dust mites, and mould as typical allergens. Patients with SAC and PAC commonly present with symptoms such as tearing, clear discharge, and itching without corneal involvement **(Figure 1)**.

In contrast, patients with AKC, VKC and GPC experience more severe symptoms, which include pain, blurry vision, and foreign body sensation. Patients with AKC and VKC often have a history of other atopic diseases and are more likely to be male.[5] AKC affects older individuals, spanning young adulthood to the fifth decade of life, with relapses and remissions showing minimal seasonal patterns. In fact, atopic dermatitis is present in 95% of patients with AKC, and 87% of patients have asthma.[5] VKC often peaks in the teenage years and occurs in warm, dry climates.[5] Patients report seasonal fluctuations, with symptoms worse in spring and often include intensified ocular pruritus. GPC is considered a non-immune reaction that is related to repeated mechanical irritation to an ocular foreign body (e.g. contact lenses, a prosthesis, or sutures from surgery).

Pathophysiology

SAC and PAC are classified as type I hypersensitivity reactions. Allergens bind to immunoglobulin E (IgE) antibodies at the mast cell surface, triggering mast cell degranulation, whereby mast cells release histamines and proinflammatory mediators including prostaglandins and leukotrienes.[1,6] Patients manifest with symptoms of allergic conjunctivitis (redness, itching, swelling, and tearing). Hours later, inflammatory cell infiltration (e.g. eosinophils, neutrophils) sustains the inflammation.[1,6]

VKC, AKC, and GPC are characterized by chronic inflammation, and might involve combined type I and IV (delayed) hypersensitivity reactions; however, the underlying mechanisms of these conditions are poorly understood.[7] In type IV hypersensitivity reactions, CD4+ T-helper 2 (Th2) lymphocytes interact with antigens, become activated, and release chemotactic factors. VKC involves Th2 lymphocytes and type 2 innate lymphoid cells, while AKC is hypothesized to include a combination of T-helper 1 (Th1) and Th2 inflammation with Th1 predominance.[7]AKC and VKC show sustained mast cell, eosinophil, and lymphocyte infiltration, which can lead to remodelling of the ocular surface with the potential for serious vision impairment.[2]

Associated Ocular Sequelae

Allergic conjunctivitis can harm vision and quality-of-life. Dry eye can exacerbate allergic conjunctivitis because these patients lack the normal quantity or quality of tears that are essential for diluting and washing away allergens, thereby increasing allergen exposure. Approximately 50% of patients with allergic conjunctivitis have dry eye, and approximately 20% of patients with dry eye have allergic conjunctivitis.[2] In addition, chronic conjunctival inflammation and membrane formation over the punctum cause eyelid issues such as punctal stenosis.[5] Keratinized lid margins lead to lid malposition (e.g. ectropion) and eyelash abnormalities (e.g. trichiasis, madarosis).[8] Severe cases of ocular surface diseases can lead to thickened, lichenified eyelids with conjunctival scarring, shortening, and adhesions (e.g. symblepharon).[9]

Vision can be affected by other causes. For example, pruritus prompts habitual eye rubbing, which elevates the risk of developing a condition termed keratoconus, in which the cornea becomes irreversibly warped, and thinned, resulting in vision loss.[10] Patients should stop rubbing their eyes, especially if they have risk factors associated with keratoconus, such as floppy eyelids or sleep apnea. Of note, inflammatory changes such as shield corneal ulcers can occur in VKC and corneal scarring and neovascularization can occur in AKC.[5] Chronic severe VKC and AKC can lead to limbal stem cell deficiency and an increased risk of contracting corneal infections, especially from *Staphylococcus aureus* bacteria and herpes simplex virus.[11] It is important to keep in mind that these complications are

Generic (Trade) Name	Class	Drug Availability (Over-the-counter, Prescription)	Canadian Age Guidelines: Dosage
VASOCONSTRICTOR			
Antazoline phosphate 0.51% (Refresh Eye Allergy Relief)	Vasoconstrictor	OTC	1–2 drops up to every 3–4 hours
Naphazoline hydrochloride 0.01–0.1% (Many, including Albalon, Clear Eyes, Collyre Bleu Laiter, Refresh Eye Allergy Relief, Opti-Tears Red Eye)	Vasoconstrictor	OTC	1 drop up to 4 times daily
Tetrahydrozoline hydrochloride 0.05% (Many, including a few Visine varieties, and Clear Eyes Triple Action)	Vasoconstrictor	OTC	≥6 years: 1–2 drops up to 4 times a day
COMBINED VASOCONSTRICTOR AND ANTIHISTAMINE			
Pheniramine maleate/naphazoline 0.3%/0.025% (Many, including Naphcon-A, Opti-Tears Allergy, Sooth Allergy previously Opcon-A, Visine for Allergy with Antihistamine, Reactine Eye Drops)	Combination first generation H1 receptor antagonist and vasoconstrictor	OTC	≥6 years: 1–2 drops up to 4 times a day
Antazoline phosphate 0.5%,/naphazoline HCl 0.05% (Refresh Eye Allergy Relief)	Combination first generation H1 receptor antagonist and vasoconstrictor	OTC	1–2 drops up to 4 times daily
MAST CELL STABILIZER			
Cromolyn sodium 2% (Cromolyn)	Mast cell stabilizer	OTC	≥5 years: 1–2 drops up to 4 times daily
Lodoxamide tromethamine 0.1% (Alomide)	Mast cell stabilizer	Rx	≥4 years: 1–2 drops up to 4 times daily
COMBINED ANTIHISTAMINE AND MAST CELL STABILIZER			
Bepotastine besilate 1.5% (Bepreve)	Selective H1 receptor antagonist and mast cell stabilizer	Rx	≥3 years: 1 drop twice daily
Ketotifen fumarate 0.035% (Zaditor, Alaway - not yet approved in Canada)	Noncompetitive H1 receptor antagonist and mast cell stabilizer	Rx (Zaditor)	≥3 years: 1 drop up to 3 times daily (Zaditor)
Olopatadine hydrochloride 0.1% (Pataday twice daily relief, previously Patanol), 0.2% (Pataday once daily relief), 0.7% (Pataday once daily relief extra strength, previously Pazeo)	Selective H1 receptor antagonist and mast cell stabilizer	Rx, OTC	≥3 years: 1–2 drops twice daily (Patanol), once daily (Pataday, Pazeo)

Table 1: *Topical pharmacotherapy for allergic conjunctivitis currently marketed in Canada[12,13] Continues on next page.*
Abbreviations: H1, histamine type 1 receptor; NSAID, nonsteroidal anti-inflammatory drug; OTC, over the counter; Rx, prescription

Generic (Trade) Name	Class	Drug Availability (Over-the-counter, Prescription)	Canadian Age Guidelines: Dosage
LOW-POTENCY CORTICOSTEROID			
Loteprednol etabonate 0.2% (Alrex), 0.5% (Lotemax, Lotemax Gel, Lotemax Ointment	Ester-based corticosteroid	Rx	≥18 years: 1–2 drops up to 4 times daily
Fluorometholone 0.1% (FML), Fluorometholone acetate 0.1% (Flarex)	Ketone-based corticosteroid	Rx	≥3 years: 1–2 drops 2 to 4 times daily, 18–65 years, (Flarex)
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS			
Ketorolac tromethamine 0.4% (Acular LS), 0.45% (Acuvail), 0.5% (Acular)	NSAID	Rx	≥3 years: 1 drop up to 4 times daily (Acular LS) ≥18 years: 1–2 drops 3 to 4 times daily (Acular, Acuvail)
Bromfenac sodium 0.07% (Prolensa)	NSAID	Rx	≥18 years: 1 drop once daily
Diclofenac sodium 0.1% (Voltaren)	NSAID	Rx	≥18 years: 1 drop up to 4 times daily
Nepafenac 0.1% (Nevanac)	NSAID	Rx	≥10 years: 1 drop 3 times daily
IMMUNOMODULATOR			
Cyclosporine 0.05% (Restasis), 0.09% (Cequa), 0.1% (Verkazia)	Calcineurin inhibitor	Rx	≥18 years: 1 drop twice daily (Restasis, Cequa) ≥4 years: 1 drop 4 times daily (Verkazia)
Tacrolimus 0.03% and 0.1% ointment (Protopic)	Calcineurin inhibitor	Rx	≥2 years: apply to eyelid or conjunctival sac twice daily (0.03%), ≥16 years (0.1%)

Table 1 (Cont.): *Topical pharmacotherapy for allergic conjunctivitis currently marketed in Canada[12,13] ; courtesy of Clara C. Chan, MD and Caberry Yu, MDAbbreviations: H1, histamine type 1 receptor; NSAID, nonsteroidal anti-inflammatory drug; OTC, over the counter; Rx, prescription*

associated with guarded outcomes.[9]

Stepwise Therapeutic Approach

Treatment of allergic conjunctivitis aims to minimize symptoms and prevent inflammation. Stepwise therapy begins with non-pharmaceutical cold compresses and progresses to different topical and oral medications **(Figure 2)**.[2] Patients should avoid known allergens if possible and stop eye rubbing, which worsens symptoms by triggering mast cell degranulation. Cool compresses provide relief, and preservative-free artificial tears dilute allergens that may be on the surface of the eye.

For SAC and PAC, common therapeutic agents include antihistamines, mast-cell stabilizers, and dual-action agents. Treatment of VKC and AKC may require topical corticosteroids and immunomodulators such as cyclosporine to suppress severe conjunctival inflammation and prevent corneal disease. For GPC, removing the causative agent (e.g. sutures with exposed knots, contact lens) is crucial. **Table 1** outlines the topical pharmacotherapies available in Canada for the treatment of allergic conjunctivitis diseases.[12,13]

Topical Antihistamine

Topical antihistamines reversibly block the H1 receptor and provide relief from redness and itching. They have limited ability to prevent the allergic reaction from occurring because they do not target mast cells, and only provide short-lasting relief.[2,4,5] Selective

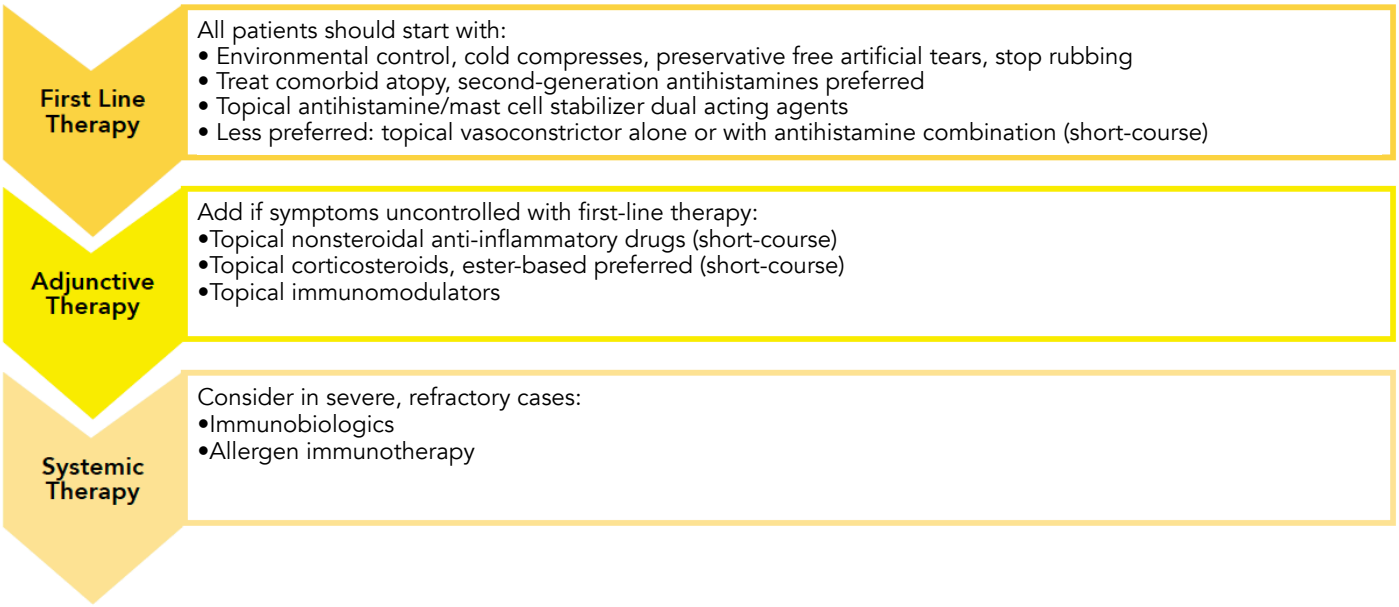

Figure 2. *Stepwise approach to management of allergic conjunctivitis; courtesy of Clara C. Chan, MD and Caberry Yu, MD*

H1 receptor targeting reduces adverse effects such as drowsiness and dryness.[14] Second-generation antihistamines such as emadastine are better tolerated due to their selectivity for H1 receptors and longer duration of effect.[5] Cetirizine ophthalmic solution 0.24% (Zerviate) has recently received FDA approval as a topical antihistamine, and has been shown to alleviate both ocular and nasal signs and symptoms associated with allergic conjunctivitis (not available in Canada).[15] Other second-generation antihistamines such as bilastine are currently being developed into a formulation that can be used as eye drops.[16]

Topical Mast Cell Stabilizers

Mast cell stabilizers inhibit mast cell degranulation, which reduces inflammation associated with late-phase allergic response inflammation.[2,4] While some patients experience symptom relief within 2 days if mast cell stabilizers are used after allergen exposure, they are rarely prescribed as a monotherapy for acute ocular allergies. This is because mast cell stabilizers are more effective as a preventive measure and are administered 3 days to 2 weeks before allergen exposure to target impending histamine release.

Topical Combined Antihistamine and Mast Cell Stabilizers

Preferred as a first line treatment, these agents combine both antihistamine properties and mast cell stabilization, providing relief within 30 minutes.[4] Side effects are mild and include cold-like symptoms, headache, and ocular stinging.[2]

Olopatadine is a commonly chosen treatment for allergic conjunctivitis, offering better relief than that of nedocromil and ketotifen. Olopatadine is only available with a prescription in Canada.[14] Bepotastine is a selective H1-antagonist that has a rapid onset of action of 3 minutes and a duration of action of up to 8 hours. Alcaftadine (not available in Canada) is a unique antihistamine that antagonizes H1, H2, and H4 receptors, which prevents recruitment of eosinophils and reduces ocular itching within 15 minutes, and this effect lasts up to 16 hours after administration.

Topical Corticosteroids

Topical corticosteroids target inflammation in both early and late stages of the allergic response, and are prescribed when the patient reports excessive and persistent signs and symptoms that interfere with quality-of-life.[2] Corticosteroids are prescribed in short courses (e.g. 2 weeks) owing to risks of associated ocular effects, including intraocular pressure (IOP) elevation, cataract formation, and opportunistic infections. Patients using topical corticosteroids for longer periods should have an ophthalmologic consultation for monitoring of side effects. Older ocular corticosteroids with a ketone group at carbon-20, (e.g., prednisolone, dexamethasone, fluorometholone) have been prescribed for severe cases of allergic conjunctivitis.[2] Recently, loteprednol etabonate (0.2% Alrex, 0.5% Lotemax), which is a newer carbon-20 ester-based corticosteroid, has become the preferred agent because it is rapidly metabolized, leading to fewer steroid-induced side effects.[17]

Topical Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs work by inhibiting the cyclooxygenase pathway, which blocks prostaglandin production from arachidonic acid.[2] NSAIDs result in reduced cellular infiltration and can improve symptoms of itching, redness, and chemosis. In addition, they pose no risk of infections, IOP increase, or cataract formation. Monitoring is essential owing to rare complications such as corneal melt and perforation.[18] Multiple NSAIDs have been

prescribed for ocular allergies, including ketorolac, diclofenac, bromfenac, and nepafenac. Only ketorolac is has received FDA approval for SAC. Topical NSAIDs are typically used as adjunctive therapy.

Topical Vasoconstrictors

Topical vasoconstrictors are adrenergic agonists that constrict blood vessels.[2,4,5] They do not reduce the underlying allergic response and are less effective for symptoms other than redness. Overuse of topical vasoconstrictors leads to rebound hyperemia due to α-1 receptor downregulation.[16] They are contraindicated for angle-closure glaucoma and in pregnancy, and are used cautiously in patients with cardiovascular disease, hyperthyroidism, and diabetes.[5,19] Combination therapy with topical antihistamines and vasoconstrictors is more efficacious than individual agents alone; however, its use can be limited due to side effects including rebound hyperemia, epiphora, and mydriasis.[2] In 2017, brimonidine 0.025%, a selective α-2 receptor agonist approved for glaucoma, received FDA approval for ocular redness. Brimonidine has a rapid onset of action, a duration effect up to 8 hours, along with a few reports of rebound hyperemia.[16]

Topical Immunomodulators

Immunomodulators such as topical cyclosporine A and tacrolimus are calcineurin inhibitors that inhibit interleukin-2 (IL-2) activation and the proliferation of lymphocytes.[2,16] Both agents are steroid-sparing alternatives and are safer for long-term use than corticosteroids for more severe allergic conjunctivitis. These agents inhibit mast cell and eosinophil activation and mediators. Cyclosporine has traditionally been approved to treat moderate-to-severe dry eye and was recently approved for treatment of VKC.[20] While not yet approved for other forms of allergic conjunctivitis, topical cyclosporine is effective for AKC and can reduce steroid dependency.[9]

Tacrolimus is a macrolide derivative that blocks T lymphocyte activity with a higher immunosuppressive potential than that of cyclosporine. Tacrolimus has been used off-label with success for treating AKC, VKC, and severe atopic dermatitis of the eyelids.[7,9] Studies have shown similar efficacy and safety profiles for tacrolimus and cyclosporine in the treatment of VKC. However, both calcineurin inhibitors have been associated with a risk of local viral or molluscum infections.[5]

Lifitegrast 5% (Xiidra) is a novel topical immunomodulator used in patients with severe dry eye. It works by inhibiting T-cell inflammation by preventing the binding of cell surface lymphocyte function-associated antigen-1 and intercellular adhesion molecule-1. Lifitegrast has high water solubility and rapid ocular tissue absorption. After promising animal studies, a phase II trial is underway to evaluate lifitegrast for allergic conjunctivitis in humans.[21]

Immunobiologics

Historically, immunobiological interventions in allergic disorders have focused on asthma, atopic dermatitis, and chronic spontaneous urticaria. Omalizumab is an anti-IgE antibody that inhibits mast cell degranulation and has shown efficacy in treating allergic rhinoconjunctivitis and treatment-resistant VKC and AKC in trials,[7] although use in rhinoconjunctivitis is off-label. Other immunobiologics targeting IL-5 are being investigated for their potential to reduce eosinophilic activity in VKC.[16]

Dupilumab, an IL-4 and IL-13 pathway inhibitor, is approved in Canada for severe, refractory atopic dermatitis, asthma, and rhinosinusitis with nasal polyps, eosinophilic esophagitis and prurigo nodularis. However, dupilumab treatment can lead to mild or moderate conjunctivitis as an ocular surface side effect, particularly in patients with preexisting allergic conjunctivitis and atopic dermatitis.[22] Most cases of conjunctivitis respond well to topical corticosteroid treatment or off-label treatment with tacrolimus 0.03%–0.1% eye drop or ointment.[7] Case reports have shown that dupilumab has been used to successfully treat patients with refractory AKC and VKC, and an ongoing clinical trial is being conducted for AKC treatment.[7]

Immunotherapy

Allergen immunotherapy includes sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT).[23] Immunotherapy is a treatment approach that can provide long-term relief from symptoms even after treatment completion. Immunotherapy has demonstrated improvement in exposure to ten- to one-hundred-fold allergen concentrations in conjunctival provocation studies. While there is more evidence for SCIT and SLIT in allergic rhinitis, their effectiveness in allergic conjunctivitis is less clear.[2] Patients may experience symptomatic improvement, but it is unclear if treatment reduces the need for topical eye drops. SCIT and SLIT are reserved for patients with IgE sensitization to aeroallergens or comorbid allergic rhinitis, especially when pharmacotherapy has failed.[23]

Oral Antihistamines

Oral antihistamines offer initial relief from allergy symptoms. First-generation antihistamines may worsen dry eye symptoms, while second- and third-generation H1 receptor antagonists have fewer sedative or anticholinergic effects and are less likely to reduce tear flow.[5] However, of the novel antihistamines, none have demonstrated superiority over the others in treating ocular allergies.[2] Second-generation oral antihistamines are often used as adjunctive therapy to topical treatment or in severe exacerbations with corneal involvement in AKC or VKC.[5]

Intranasal Corticosteroids

Intranasal corticosteroids such as fluticasone and mometasone may reduce symptoms of allergic conjunctivitis, although they are mainly prescribed for allergic rhinitis owing to concerns about IOP elevation.[16] A recent study has shown an increase of 0.8% in the incidence of elevated IOP compared to placebo, with no increase in glaucoma rates.[24]

Future Therapeutic Targets

Reproxalap 0.25% is an investigational reactive aldehyde species modulator that has shown reduced ocular itching, tearing, and redness in a phase III clinical trial.[25] The FDA has accepted the New Drug Application for Reproxalap for treating dry eye disease. Other medications under investigation have limited evidence for treating ocular allergies. These include glucocorticoid receptor agonists, various immune receptor antagonists (e.g. C-C chemokine receptor type 3, C-C chemokine receptor type 2, IL-1, integrin), Janus Kinase inhibitors, tyrosine kinase inhibitors, and resolvins.[16]

Several novel devices are under study that include drug delivery systems, such as ketotifen-eluting contact lenses for antiallergic and vision-correction purposes, epinastine-hydrochloride-releasing soft contact lenses, and solid lipid nanoparticles to increase bioavailability.[16] The FDA has approved dexamethasone ophthalmic insert at a dose of 0.4 mg (Dextenza), which is a physician-administered intracanalicular device for treating ocular itching in allergic conjunctivitis.[26]

Conclusion

Allergic conjunctival diseases require safe and effective treatment to reduce symptoms and improve quality-of-life. Topical dual-acting antihistamines and mast cell stabilizers are the mainstay of pharmacotherapy for patients with allergic conjunctivitis. During severe exacerbations, short courses of topical corticosteroids are recommended. For severe and chronic forms of ocular allergies, such as VKC and AKC, topical immunomodulators are effective steroid-sparing alternatives. Proper diagnosis and treatment with a collaborative approach involving the allergist, dermatologist, and eye-care specialist is essential to prevent vision-threatening complications.

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Financial Disclosures:

None declared

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