Interprofessional Management of Allergic Conjunctivitis: A Proposed Algorithm for Canadian Clinical Practice

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Abstract

Ocular allergies affect a large and increasing number of people in North America. Canada's statistics are likely to mirror those of the U.S., where up to 40% of the population is affected by ocular allergies. The symptoms and signs of ocular allergies can greatly affect productivity and have a dramatic effect on overall quality of life (QoL). Over the years, many effective treatments have been developed for the management of ocular allergies. For allergic conjunctivitis, topical ophthalmic agents include antihistamines, mast-cell stabilizers, dual-activity agents, steroids, nonsteroidal anti-inflammatory drugs, and other immune-modulating drugs. Oral antihistamines are commonly chosen by patients for all forms of allergy, including allergic conjunctivitis. This review provides a summary of the forms of ocular allergy, with a particular focus on the symptoms and signs, diagnosis, current treatment options, and impact on QoL. More importantly, through multidisciplinary collaboration, a simplified treatment algorithm is proposed for Canadian clinical practice. This algorithm provides practitioners the best possible management strategies based on an individual patient presentation, thereby maximizing treatment efficacy and minimizing the effects on tasks of daily living and QoL.

KEYWORDS
Allergic Conjunctivitis; Ocular Allergy; Antihistamines; Ophthalmic Steroids; Dual-activity Agents

INTRODUCTION

Ocular allergies such as allergic conjunctivitis are a growing problem in Canada; up to 40% of the population is presumed to be affected.[1-8] Ocular discomfort associated with allergic conjunctivitis has been reported in about 15% of primary health care office visits for eye-related issues.[9] More importantly, ocular symptoms occurring for at least one day were reported in 90% of patients who had allergic rhinitis.[10] Approximately 40% of patients with allergic rhinitis and conjunctivitis have asthma, and 80% of those with asthma have allergic conjunctivitis.[11,12] This highlights the importance of an appropriately targeted case history, as ocular signs and symptoms may not be present at the time of visit. Despite the prevalence of ocular allergies, many patients are underdiagnosed and undertreated, since the prevalence and complexity of the disease and its clinical treatment may not be fully appreciated.[13]

Further, the signs and symptoms of ocular allergies can greatly affect productivity at school and work, as well as quality of life (QoL).[1,14] Over the years, many effective agents have been developed for the treatment of ocular allergies.[2,15] However, many patients with ocular allergies self-treat or do not seek specific ophthalmic care, which often leads to ineffective treatment and inadequate symptom relief. Therefore, professional eye care is important for determining appropriate treatments that target both the symptoms as well as the tissue damage secondary to acute and chronic allergic ocular inflammation.

This review provides an overview of allergic conjunctivitis, the most common form in the spectrum of ocular allergic diseases, by discussing the symptoms and signs, diagnosis, current available treatment options, and impact on QoL. More importantly, a simplified treatment algorithm is proposed to guide the practitioner to the most appropriate initial and subsequent treatment option(s) for allergic conjunctivitis tailored to individual patients, thereby improving patient management and allowing for maximal symptom relief as well as tissue normalization. In addition, considerations for interprofessional collaboration are outlined to facilitate best practices and ensure patient satisfaction.

INFLAMMATORY RESPONSE IN ALLERGIC CONJUNCTIVITIS

Due to its large surface area, the conjunctiva is one of the most accessible mucosal surfaces for airborne allergens and thus is a common site for the initiation of allergic inflammation. Allergic conjunctivitis is mainly a type I allergic reaction in which mast cells, along with basophils, play a major role.[15-18] Mast cells are primed when B-cells are activated by allergen exposure. On re-exposure, the pathophysiological processes of type I allergic reactions are triggered immediately; some symptoms begin within minutes. Activated mast cells cause an inflammatory response both by releasing pre-formed intracellular mediators (such as histamine, bradykinin, and cytokines), and by generating newly formed mediators (such as leukotrienes and prostaglandins) from membrane phospholipids and the arachidonic acid cascade.[2,15,17,18] In ocular tissues, histamine–the main mediator of the immediate response–induces itching, redness, tearing, chemosis, eyelid edema, and a papillary reaction (Figures 1–4).[2,15,16,18] In the later phase of type I allergic reactions, leukotrienes and other chemotactic factors recruit new inflammatory cells (e.g., eosinophils, neutrophils, basophils) which secrete secondary inflammatory and allergic mediators to further provoke and exacerbate ocular inflammation, thus increasing the chronicity of the condition, as well as the likelihood of tissue damage.[1] As the tears drain through the nasolacrimal duct to the nose, allergens (as well as any medications applied to the ocular surface) are drained directly into the nasal passages.

TYPES OF ALLERGIC CONJUNCTIVITIS AND OTHER ALLERGIC EYE DISEASES

Allergic conjunctivitis can be classified into two types, seasonal and perennial, with seasonal allergic conjunctivitis (SAC) being the more common of the two.[15-17] SAC and perennial allergic conjunctivitis (PAC) are similar conditions that differ in the causative allergens and their exposure period.[1] SAC is triggered by airborne allergens, such as mold, tree, grass, and weed pollens, that have a seasonal periodicity and are most abundant in spring, summer, and fall.[15,17] PAC occurs year-round and is caused by allergens commonly found in the household, such as dust mites, mold spores, or animal dander.[15,17]

Although allergic conjunctivitis is by far the most common ocular allergic disease, other chronic ocular allergic conditions may cause more severe symptoms, which can lead to tissue damage and, in rare cases, vision loss. These conditions include atopic keratoconjunctivitis (AKC; Figure 5a) and vernal keratoconjunctivitis (VKC; Figure 5b).[15,17] Atopic dermatitis may also occur on the eyelid (Figure 5c). The main characteristics of these conditions are described in Table 1.

Figure 1: *Acute SAC. On the left (patient's right), a normal eye not exposed to allergen. On the right (patient's left), an eye displaying an acute allergic response within 20 minutes after direct exposure to grass allergen. SAC = seasonal allergic conjunctivitis.*

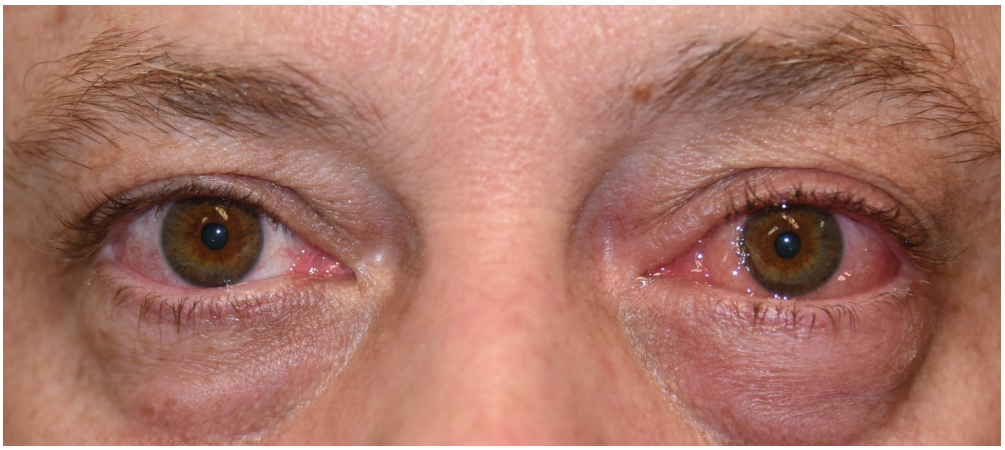


Figure 2: *Acute SAC. (a) Tearing, and (b) conjunctival injection and chemosis secondary to exposure to grass allergen. SAC = seasonal allergic conjunctivitis.*

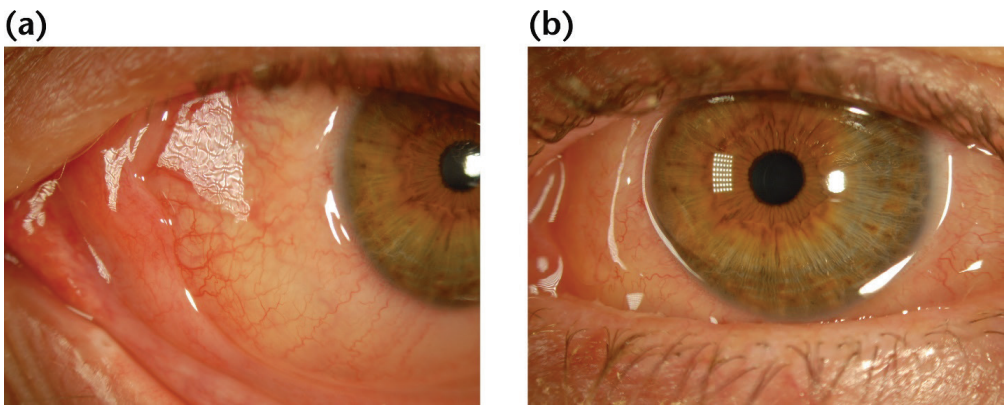


Figure 3: *Chronic PAC (dust allergy). Superior tarsal papillary conjunctivitis shown with (a) white light, and (b) fluorescein and cobalt blue light. PAC = perennial allergic conjunctivitis.*

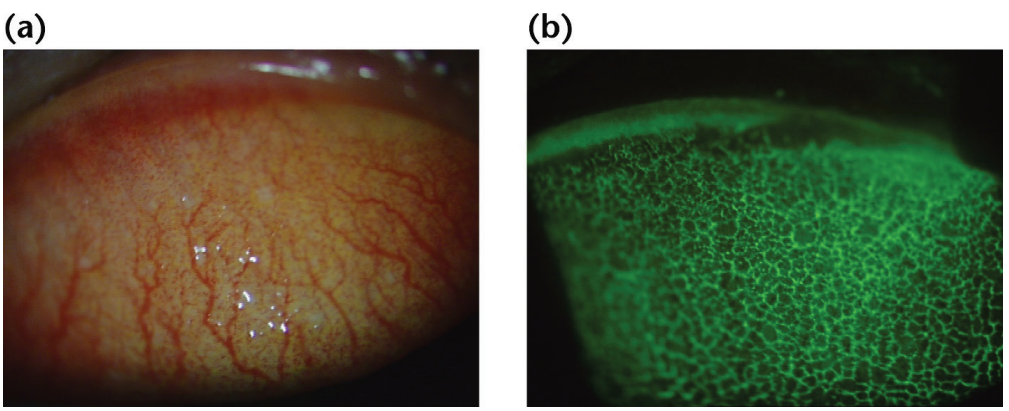


Figure 4: *Chronic PAC (dust allergy). Superior tarsal papillary conjunctivitis shown with (a) fluorescein and cobalt blue light, and (b) white light. (c) Inferior tarsal papillae shown with fluorescein and cobalt blue light. PAC = perennial allergic conjunctivitis.*

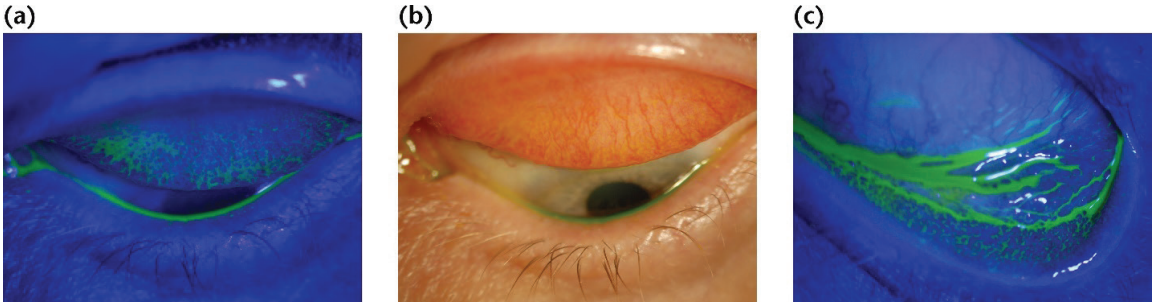


Figure 5: *Ocular signs of (a) AKC, b) VKC, and (c) atopic dermatitis. AKC = atopic keratoconjunctivitis; VKC = vernal keratoconjunctivitis. (a) and (b): Courtesy of Dr. Gina Sorbara, executive of IACLE, with permission.*

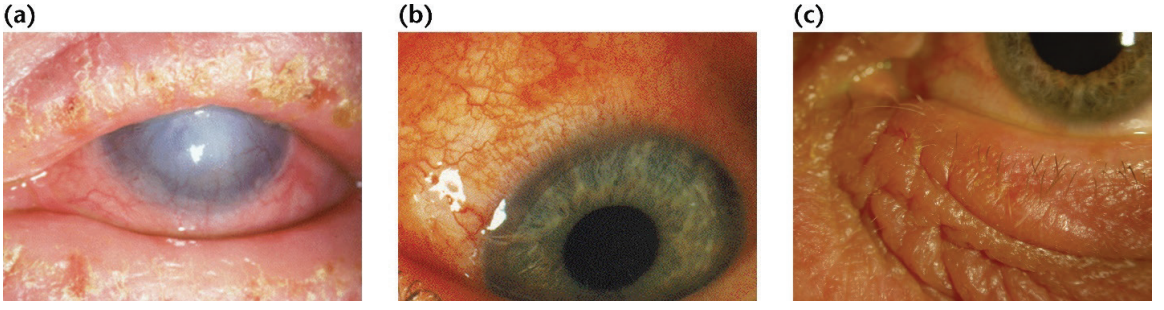


Table 1: *Other ocular allergy subtypes and their main characteristics*

Ocular allergy subtype	Demographics and/or associations	Primary symptoms
Atopic keratoconjunctivitis (AKC)	• Typically occurs in males, 30–50 years of age[15] • Perennial, can be worse in the winter months • Associated with atopic dermatitis/eczema[15,17] • Associated with other allergic diseases (e.g., hay fever, asthma)[15,17]	• Severe ocular itching (ocular surface, eyelids) • Other symptoms (similar to VKC): Tearing, burning, photophobia, mucous discharge • Significant hyperemia and edema of the conjunctiva (chronic inflammation)[15] • Corneal scarring, neovascularization
Vernal keratoconjunctivitis (VKC)	• Typically occurs in males, 3–25 years of age[15] • History of atopy such as asthma, allergic rhinitis, and eczema in half of those with VKC[19]	• Severe ocular itching • Other symptoms: Photophobia, tearing, and mucous discharge[15] • Limbal nodules, Trantas' dots (limbal form)[15] • Large cobblestone papillae on superior tarsus (chronic inflammation)[15] • Shield ulcer may form in severe cases[15]
Atopic dermatitis	• Can occur in the general population • Often begins in early childhood[20]	• Itching, dryness of the skin, and superficial inflammation[21]

CHARACTERISTICS OF ALLERGIC CONJUNCTIVITIS – IMPACT AND DIAGNOSIS

Importance of appropriate professional care

Despite the very high prevalence of ocular allergies and the increasing awareness of the disease, more than one-third of patients are underdiagnosed and therefore undertreated.[13,14,17,22] Allergy symptoms are often regarded as less worthy of directed attention and treatment compared to chronic, life-threatening diseases.[13] Further, patients often self-diagnose and therefore fail to seek professional care, even when relief from over-the-counter (OTC) therapies proves to be inadequate.[14] Patients who self-treat may not realize that prescription treatments with enhanced potency and selectivity are available and that they can be specifically tailored to their symptoms and signs. Consequently, products purchased OTC are often less effective (e.g., topical vasoconstrictors) or have unintended adverse effects (e.g., drying effect from most oral antihistamines; rebound vasodilation from topical vasoconstrictors). Of further concern is the use, and overuse, of OTC products that carry the risk of exacerbating ocular surface conditions. For example, when dry eye disease and allergic conjunctivitis coexist, not only are topical OTC products unlikely to be effective, but the preservatives may further cause ocular surface toxicity, thus exacerbating the symptoms and signs of both conditions. It follows that if such inappropriate treatment is common amongst patients, without education by eye or healthcare providers, many will also be unaware of the potential for relief of nasal symptoms from prescription topical ophthalmic drugs, and conversely, the potential for relief of ocular symptoms from nasal preparations.[23]

While many practitioners see patients with ocular symptoms, professional evaluation with slit-lamp biomicroscopy and directed physical examination techniques are required to rule out comorbidities and to differentiate allergic conjunctivitis from other red-eye and ocular surface diseases, which require alternate/additional treatment considerations.[16,24] While topical ophthalmic corticosteroids are a critical component of therapy for allergic conjunctivitis, treatment with any form of long-term steroid (topical, oral, or inhaled) necessitates frequent eye examinations by an eye care professional due to the increased risk of elevated intraocular pressure (IOP), cataract formation, and central serous chorioretinopathy.[25-28] The reverse is also true: those with non-ocular symptoms/signs or with uncontrolled allergic conjunctivitis, despite maximal medical therapy, may require referral to a primary care practitioner or an allergist to investigate other treatment options (e.g., immunotherapy). Referral to an optometrist, a primary care provider, or an allergist will be discussed later in this review.

Symptoms and signs

The most prominent symptom of allergic conjunctivitis is itching, which can range from mildly uncomfortable to severely debilitating, or may even be described as painful.[15-17,29] Other symptoms include redness, tearing, soreness, foreign body sensation, burning/stinging, and lid swelling.[15-17,29] As both eyes are generally exposed to allergens at the same time, bilateral involvement is common. Of course, eye and lid itching and redness may be symptoms of other ocular diseases; thus, a thorough history and physical examination, including slit-lamp examination, are critical to ruling out these conditions.[7,30] Since nasal and ocular mucosal tissues react to allergens in a similar way and since these structures are connected, it follows that allergic conjunctivitis has been positively correlated with allergic rhinitis.[22,29,31,32]

Assessment of allergic conjunctivitis

Most patients with allergic conjunctivitis show a straight-forward presentation. However, others have known or unknown comorbidities, or present diagnostic challenges, such as symptoms or signs that overlap those of other conditions, thus necessitating a team-based care approach. To determine the appropriate management strategies for patients with ocular allergies, it is important to have an accurate diagnosis.

Patient history

While ocular itching is the hallmark of ocular allergies, queries regarding a patient's personal history such as redness, tearing, soreness, foreign body sensation, burning/stinging, pain, and swelling are also important. Further, since ocular itching is reported in several other ocular conditions, such as Staphylococcal and demodex-related blepharitis, toxicity from treatments and preservatives, as well as other forms of dry eye disease,[33] this symptom alone is inadequate to determine that a patient has an ocular allergy.

Moreover, it should be emphasized that patients with dry eye disease also report ocular itching.[15] The primary symptoms of dry eye disease include burning, stinging, and foreign body sensation.[15] The differentiation between itching and burning may be an important key to the identification of dry eye disease.[15] If patients feel the desire to

scratch their eyes, it is usually a case of ocular allergy. Alternatively, a lesser degree of "itching" should be identified as burning/stinging, which is associated with dry eye disease.[15]

Risk assessment includes past/current medication use, history of other comorbidities (e.g., atopic dermatitis), and family history. Patients with one or both parents with allergies have a higher risk of developing allergies compared to those with no family history. Indeed, the risk of having allergic rhinitis is increased by 20% in individuals with a parent having the same allergic disease.[34] Hence, it is key for practitioners to ask patients about their family's allergy history. Table 2 summarizes the queries regarding the personal history of a patient suspected to have an allergic disease.

Table 2: *Case-specific history in patients suspected to have allergic disease*

Category	Questions for patients
Ocular history	• What are the symptoms, and how severe are they (mild/moderate/severe)? • When did they start? • Have there been previous episodes? • Is presentation unilateral or bilateral? • Are the eyes itchy? How itchy (mild, moderate, or severe)? What time of day is it the worst? • Is there eye-rubbing? If so, how? • Do the eyes hurt? Burn? Sting? Does it feel like there is something in the eye(s)? • Is there any discharge? If yes, is it watery or mucoid? • Is vision affected? • Is there photophobia? • Are there exacerbating or relieving factors? • Do the symptoms vary with season? Environment? • Are the eyes dry? • Are contact lenses worn?
Health history	• Is there associated rhinitis? Asthma? Atopic dermatitis? • Frequent "colds" (may be persistent rhinitis)? • Is there a family history of allergy (rhinitis, hay fever, asthma, or atopic dermatitis)? • Are there any food or drug allergies? • Any medications? • Diagnosis of attention deficit hyperactivity disorder (ADHD)?[35]
Exposures / Environment	• Does the patient have pets? • Is the patient's home carpeted? Forced-air heating? Air conditioning? • Does the patient smoke or live with a smoker? • Have there been new exposures (i.e., new pet, renovations, or new personal or home hygiene products)? • Has there been contact with others with a red eye (possibility of infectious cause)?
Treatment	• Has an OTC topical product been used? If so, which product(s)? • Has an OTC oral agent been used? If so, which product(s) (first- or second-generation)? • How often has the product(s) been used, and for how long? • Has there been any relief of symptoms? Is it worsening?
QoL	• Are patient's symptoms affecting his/her ability to study/work? • Is the patient having difficulty with reading, concentration, driving, or sleep? • Has school/work been missed due to symptoms?

Modified from Small P and Kim H. Allergic rhinitis. Allergy Asthma Clin Immunol 2011;7(Suppl 1):S3.[36]
OTC = over-the-counter; QoL = quality of life

Physical assessment

Physical examination for those at risk involves gross assessment as well as detailed slit-lamp biomicroscopy of the periocular and ocular tissues. Examination should include assessment of the lids and lashes, lid margins and Meibomian glands, bulbar and palpebral conjunctiva, tears (tear prism, volume, stability, osmolarity), and cornea, as well as ocular surface staining (fluorescein, lissamine green).[2,16]

All tissues of the ocular surface may be affected in allergic conjunctivitis. Conjunctival injection may be mild to moderate in patients with allergic conjunctivitis, but tends to be superficial. Chemosis may seem out of proportion to the degree of redness, producing a balloon effect, or may be observed only as a milky or glassy appearance of the bulbar conjunctiva. Both may be most noticeable towards the plica semilunaris.[2] A papillary response is expected on the palpebral conjunctiva; however, it may be masked by allergy-associated chemosis.[1] The eyelids may be hyperemic or edematous, and specific observations of allergy masqueraders such as blepharitis should be documented.[2,16] Table 3 lists the ocular examination findings related to allergic conjunctivitis.

Table 3: *Ocular examination findings related to allergic conjunctivitis*

Ocular structure	Ocular signs
Lids/lashes	• Lid redness/edema
Bulbar conjunctiva	• Superficial bulbar redness • Chemosis
Tarsal conjunctiva	• Tarsal redness/papillae
Cornea	• Clear cornea
Tears	• Tearing, mucoid strands

The chronic forms of allergic conjunctivitis are related to late-phase type I allergic responses and are more likely to show severe forms of inflammation related to tissue damage. Signs detected during slit-lamp biomicroscopy, such as giant papillae, corneal infiltration, pannus, neovascularization, and ulceration, point to the severity of the disease, but also may alert the practitioner to other disease types such as AKC, VKC, and type IV hypersensitivity. Signs such as redness can be indicators of allergic conjunctivitis, dry eye disease, and infectious conjunctivitis. While redness is not a differentiator of diagnosis, severe redness may indicate the presence of infectious conjunctivitis. Other symptoms/signs (e.g., presence of mucus and discharge, which may be an indicator of infectious conjunctivitis caused by a virus) should be considered during the diagnosis of allergic conjunctivitis and an additional examination should be done. Patients with allergic conjunctivitis also often display nasal symptoms, which are likely associated with allergic rhinitis. Table 4 lists the ocular examination findings related to other ocular comorbidities.

Table 4: *Ocular examination findings related to common ocular comorbidities*

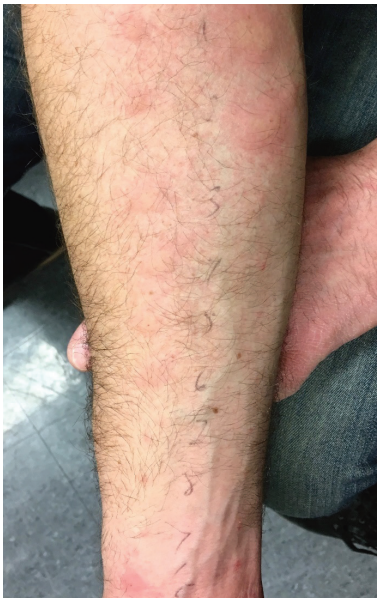
Ocular structure	Ocular signs	Related ocular disease states
Lids/lashes	• Lash debris, lid hypertrophy, injection	• Blepharitis (demodex, staphylococcal, seborrheic) • Evaporative dry eye disease
	• Periocular scaly, dry skin	• Atopic dermatitis
Bulbar conjunctiva	• Redness, conjunctival chalasis	• Dry eye disease
Tarsal conjunctiva	• Large papillae	• VKC
Cornea	• Limbal infiltrates, Tantra′ dots, neovascularisation	• AKC
	• Pannus, shield ulcer	• VKC
Tears	• Tearing, profuse mucous discharge	• VKC
	• Inadequate tear volume, low tear meniscus, excess evaporation (poor stability), hyperosmolarity	• Dry eye disease

AKC = atopic keratoconjunctivitis; VKC = vernal keratoconjunctivitis

Allergy testing

When allergic conjunctivitis is suspected, an allergy assessment should be considered. The standard method of allergy testing is aeroallergen skin prick testing (Figure 6).[36] This type of testing has high sensitivity, so it is a useful screening test for allergic conjunctivitis. Common aeroallergens are applied to the forearm or back and the skin is slightly pricked. If there is a wheal and flare that is larger than the negative control, then the test is positive and allergic conjunctivitis is the likely cause of symptoms. Skin prick testing rarely causes systemic allergic reactions. If skin prick testing cannot be performed, serum IgE testing for the aeroallergens should be considered.

Figure 6: *Patient's forearm undergoing aeroallergen skin prick testing. If there is a wheal and flare that is larger than the negative control, then the test is positive and allergic conjunctivitis is the likely cause of symptoms.*



Impact on QoL

Symptoms such as ocular itching, redness, and tearing can cause significant distress in moderate to severe allergic conjunctivitis.[16,25] Most patients with allergic conjunctivitis report that ocular symptoms are at least as bothersome as nasal symptoms.[14,37] A report from the World Allergy Organization noted that allergic conjunctivitis carries the same "clinical gravity" as allergic asthma and rhinitis.[23]

During allergy season, many patients are not comfortable being outdoors and find that their allergy symptoms interfere with tasks of daily living. Allergic conjunctivitis has been reported to interfere with reading (>70%), concentration (58%), driving (60%), and sleep (>50%).[3,17,38,39] Discomfort and fluctuating vision may also lead to intolerance to contact lens wear.[40]

While considered to be a benign disease, allergic conjunctivitis is often overlooked, underdiagnosed, or inadequately treated. Self-treatment with OTC agents may not provide adequate relief and may add to the negative impact of allergic conjunctivitis on QoL. Timely and appropriate involvement of both eye care and medical practitioners is essential to successfully manage this common disease. The need for early and aggressive treatment of allergic conjunctivitis is akin to that for other allergic diseases such as asthma and atopic dermatitis, whereby addressing the inflammation effectively reduces not only long-term ocular symptoms and signs, but also possibly reduces the induction of responses in the nasal cavities and other tissues. The notion to "hit early and hit hard" may be applicable to allergic conjunctivitis and other ocular allergic conditions, as with atopic dermatitis and asthma.[21]

MANAGEMENT STRATEGIES FOR ALLERGIC CONJUNCTIVITIS

To date, the only disease-modifying treatment available for allergic diseases including conjunctivitis is immunotherapy, which allows for desensitization to the offending allergens.[2] However, management strategies are changing

rapidly; many new treatments are being developed and established agents are being applied differently. Eye care practitioners, primary care providers, and allergists have a growing selection of topical agents from which to choose, with the principal goal of relieving and controlling the symptoms and signs of allergic conjunctivitis. Though the initial therapy is often empiric, diligence in teasing out details in the presentation of each individual patient can provide guidance to the most appropriate strategies, including the time-course of treatment. Appropriate management of the condition necessitates interrupting the inflammation cycle early and aggressively with the hope of preventing further triggering of the inflammatory cascade in affected and adjacent tissues.

Non-pharmacological measures

Awareness of the distribution and density of common allergens can help patients with symptom management.[2] While allergen avoidance may improve allergic conjunctivitis, it is often difficult to achieve.[2,15,17] However, dust mite- or animal dander-control measures are recommended in the case of these perennial offenders. Air conditioner use with windows closed can help prevent and remove airborne allergens from the home or office environment for both seasonal and perennial sufferers.[2,17] The contact lens modality may be switched to daily disposable lens types, and wearing time can be reduced.[2]

To relieve mild ocular allergy symptoms, cold compresses may be applied to the eyes, and/or OTC lubricating drops may be instilled to dilute and wash away allergens.[2,15,17] However, non-pharmacological measures remain supportive only and have minimal effects except for very mild or infrequent symptoms. There is little confirmatory evidence that these measures alone can improve clinical outcomes.

Oral and topical antihistamines

Oral antihistamines are important for the treatment of allergy. These agents are readily accessible to patients OTC or with a prescription. However, their use in allergic conjunctivitis should be considered with caution because of both systemic and ocular adverse effects.[18] First-generation oral antihistamines have high lipid-solubility that allows these agents to penetrate the blood-brain barrier and can cause adverse effects such as sedation, dry mouth, dry eye, hypotension, and tachycardia.[15,18,41] Second-generation agents are preferred as they have lower lipid-solubility, which diminishes the chances of these effects.[18] Patients taking sedating antihistamines should not be working with dangerous machinery or driving.[18] In patients with concomitant conditions such as peptic ulcers or with anterior chamber angles that are considered to be capable of pupillary block angle-closure, caution should be exercised with antihistamines that have strong anticholinergic properties (e.g., diphenhydramine).[18]

Generally, topical ophthalmic antihistamines are better tolerated than oral antihistamines both because they reach the target tissue quickly, which allows for a more rapid onset of action, and because they are absorbed less systemically, which allows for reduced adverse effects.[18,42] Ocular dryness is not an issue with topical agents because of their route of administration. Earlier-generation topical antihistamines included antazoline and pheniramine, which are still available OTC in combination with the vasoconstrictor naphazoline (Table 5).[15,18] These preparations can cause adverse reactions such as stinging on instillation.[54] Later-generation topical antihistamines, such as levocabastine (Livostin) and emedastine (Emadine), though much more selective and effective,[18] have a short duration of action, necessitating frequent instillation. Topical ophthalmic antihistamines are acute-care drugs only, and therefore are not effective at stabilizing the ocular tissues to antigen presentation.[15]

For these reasons, along with the development of more effective agents, topical ophthalmic antihistamines are rarely used alone.

Topical mast-cell stabilizers

Topical mast-cell stabilizers prevent the degranulation of mast cells associated with a type I allergic reaction, thus reducing the influx of other inflammatory cells. Studies have reported that, compared to placebo, mast-cell stabilizers are effective for reducing itching and tearing.[17,55,56] For example, in one study, patients who received mast-cell stabilizers 1–2 weeks before allergy season reported more days without any ocular itching compared to patients who received placebo.[56] While single-acting mast-cell stabilizers may be effective if used long before allergen exposure, they are chronic-care medications that are not helpful for treating the acute phase of allergic conjunctivitis.[15,17,57] Examples of mast-cell stabilizers include nedocromil (Alocril), lodoxamide (Alomide), and sodium cromoglycate 2%, the latter of which is OTC (Table 5). Again, mast-cell stabilizers are rarely used alone due to the availability of more effective agents.

Topical dual-activity antihistamines/mast-cell stabilizers

Topical dual-activity agents are currently regarded as the standard of care and the first-line treatment for allergic conjunctivitis.[25] These agents have the combined mechanisms of both antihistaminic and mast-cell stabilizing activity, enabling the immediate action of the former and the long-term benefits of the latter.[15,18] Examples of dual-activity agents include ketotifen 0.025% (Zaditor), olopatadine 0.1% (Patanol), 0.2% (Pataday), and 0.77% (Pazeo), as well as bepotastine besilate 1.5% (Bepreve; Table 5).

Topical dual-activity agents are well tolerated and demonstrate a more rapid onset and longer duration of action in reducing the itch associated with allergic conjunctivitis when compared with single-acting antihistamines.[44,46] Unfortunately, data comparing oral antihistaminic agents to topical agents is relatively sparse.[58] In a randomized trial comparing topical ketotifen 0.025% to an oral antihistamine, subjects who received topical ketotifen 0.025% reported significantly lower itching and redness scores within minutes after instillation during the conjunctival allergen challenge (CAC).[44]

Topical dual-activity agents are the work-horses of allergic conjunctivitis, with support from many clinical studies as well as years of clinical use. Olopatadine has been shown to give significantly lower ocular itching and hyperemia scores, as well as tear histamine levels compared to placebo in patients with allergic conjunctivitis.[29,59] Olopatadine has also been shown to improve nasal symptoms, eyelid swelling, and chemosis with topical ophthalmic administration, as well as to improve ocular symptoms with nasal administration.[45] Olopatadine 0.1% has been compared with ketotifen 0.025% in various randomized studies.[60-62] Two studies reported that olopatadine 0.1% was more effective than ketotifen 0.025% at relieving symptoms and signs of allergic conjunctivitis, and a majority of patients preferred olopatadine 0.1% over ketotifen 0.025% based on efficacy and ocular comfort.[60,62] Other studies in the U.S. have compared olopatadine to epinastine, azelastine, and alcaftadine, but these agents are not available in Canada.

The newest dual-activity agent to the North American market is bepotastine besilate 1.5% (Bepreve). It is the first new anti-allergic agent to the Canadian market for almost two decades. While demonstrating a similar mechanism of action, bepotastine besilate differs in its bioavailability, selectivity for the H1 histamine receptor, and onset of action. In two randomized controlled studies, a rapid response was observed within 3 minutes post CAC and also when allergen exposure occurred at 15 minutes or 8 hours after instillation, thus demonstrating both acute and prolonged effects.[46,47] Symptom relief was rapid and sustained even for patients with severe symptoms.[48,49,63] Bepotastine besilate was shown to be equally effective in the morning and in the evening for relief of both ocular and itchy/runny nose symptoms, whereas in the same study, olopatadine 0.2% was only effective in the morning.[8] At the end of the randomized cross-over study, significantly more patients (63.3%) preferred bepotastine besilate to olopatadine 0.2%.

Topical steroids

Steroids are known to target most aspects of the inflammatory cascade. Certainly, steroids are critical in the management of chronic ocular allergic diseases such as VKC and AKC, where disease control and tissue damage are concerns. However, these agents are also helpful in allergic conjunctivitis by suppressing mast-cell proliferation, inhibiting cell-mediated immune responses, and blocking the production of all inflammatory chemical mediators.[15,64] Patients with moderate to severe SAC benefit most from ophthalmic steroids, as well as those who experience repeated allergen exposures and prolonged symptoms and signs.

Despite the benefits of topical steroids, these agents are generally used on a short-term basis due to the risk of adverse effects including elevated IOP and cataracts.[15,27] Therefore, patients treated with steroid therapy should be closely monitored. Examples of topical steroids include ester-based steroids (loteprednol etabonate 0.2% [Alrex] and 0.5% [Lotemax]), and ketone-based steroids (fluorometholone 0.1% [FML], prednisolone acetate 1% [Pred Forte], phosphate 1%, and dexamethasone 0.1%). Ester-based steroids are as effective as ketone-based steroids, but have chemical properties that allow unbound drug molecules to be rapidly metabolized, thus lowering the risk of steroid-induced adverse effects.[64,65] The term "soft" steroid is often used in association with ester-based formulations; however, it should be clear that this refers to the mitigated adverse effect profile and not the effectiveness of this molecule. Combined with their established safety profile, ester-based steroids are an ideal choice for the treatment of inflammation associated with all ocular allergic conditions.

Loteprednol etabonate 0.2% is the only ester-based steroid that is indicated for temporary relief of the signs and symptoms associated with SAC (Table 5).[2] Studies have demonstrated that this agent has favourable efficacy and safety profiles, and provides a statistically significant reduction in redness and ocular itching in patients with SAC.[51,52] Rates of adverse effects are very low; indeed, in three studies, only 1% of patients in both the treatment and placebo groups showed a significant rise in IOP (≥10 mmHg),[51,52] and no association was found with long-term use or cataracts.[64]

Table 5: *Topical agents available in North America for the treatment of allergic conjunctivitis*

Agents (Brand name)	Availability*	OTC/Rx	Year of market availability†	Age indication‡	Dosing schedule
Ocular antihistamines antazoline (only found in combination)[15,17,18]	Both	OTC	Before 1980	N/A§	QID
pheniramine (only found in combination)[15,18]	Both	OTC	Before 1980	N/A§	QID
levocabastine (Livostin)[43]	Both	Rx	1995	≥ 12 years	BID
emedastine (Emadine)[17,18]	U.S. only, currently cancelled post market in Canada	Rx	1998	≥ 12 years >3 years	QID
Mast-cell stabilizers nedocromil (Alocril)[15,17]	Both	Rx	2000	>3 years	BID
lodoxamide (Alomide)[15,17]	Both	Rx	1992	>4 years	QID
sodium cromoglycate 2%[15,17]	Both	OTC/Rx	1993	>5 years	QID
Dual-activity agents ketotifen 0.025% (Zaditor)[15,17,44]	Both	Rx	2000	>3 years	BID
olopatadine 0.1% (Patanol)[15,17,29,45]	Both	Rx	1998	≥3 years	BID
olopatadine 0.2% (Pataday)	Both	Rx	2011	≥18 years	QD
olopatadine 0.77% (Pazeo)	Both, but not yet released in the Canadian market	Rx	2017	≥2 years	QD
bepotastine besilate 1.5% (Bepreve)[46-49]	Both	Rx	2017	>3 years	BID
epinastine 0.05% (Elestat)[15,17]	U.S. only	Rx	2004 (U.S.)	>3 years	BID
alcaftadine 0.25% (Lastacaft)[50]	U.S. only	Rx	2014 (U.S.)	>2 years	QD
azelastine 0.05% (Optivar)[15]	U.S. only	Rx	2000 (U.S.)	>3 years	BID
Ophthalmic steroids loteprednol etabonate 0.2% (Alrex)[15,51,52]	Both	Rx	2009	>18 years	QID
loteprednol etabonate 0.5% (Lotemax)**	Both	Rx	2009	>18 years	QID
fluorometholone acetate 0.1% (FML)**	Both	Rx	Before 1980	>2 years	BID††
prednisolone acetate 1.0% (Pred Forte)**	Both	Rx	Before 1980	All ages	BID††
NSAIDs ketorolac 0.4% (Acular LS)**[15,17,53]	Both	Rx	1992	≥18 years	QID
diclofenac 0.1% (Voltaren Ophtha)**[17]	Both	Rx	1991	≥18 years	QID
nepafenac 0.1% (Nevanac)**	Both	Rx	2008	≥18 years	TID
bromfenac 0.7% (Prolensa)**	Both	Rx	2015	≥18 years	QD
Calcineurin inhibitors cyclosporin emulsion 0.05% (Restasis)	Both	Rx	2010	N/A§	BID
tacrolimus 0.1% and 0.03% (Protopic)‡‡	Both	Rx	2001	For ages 2–15, only 0.03% strength is indicated	BID

* "Both" indicates that the agent is available in both Canada and the U.S.
† Unless otherwise stated, the year of market availability is for the Canadian market.
‡ For agents that are available in both Canada and the U.S., the age indication is based on the Canadian product monograph.
§ Information not available.
** Off-label use only in Canada.
†† Or according to the severity of inflammation.
‡‡ These products are used only external to the eyes.
BID = twice daily; N/A = not available; NSAIDs = nonsteroidal anti-inflammatory drugs; OTC = over-the-counter; QD = once daily; QID = four times a day; Rx = prescription; TID = three times a day

While topical ophthalmic steroids are critical for the treatment of allergic eye diseases, nasal steroids used in the treatment of allergic rhinitis (e.g., mometasone furoate) have also been shown to improve ocular allergy symptoms.[31]

Topical ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs)
Topical ophthalmic NSAIDs are used primarily in perioperative cataract care, but have also been found to reduce symptoms associated with allergic conjunctivitis. NSAID molecules interfere with the induction of newly formed inflammatory mediators in type I allergic reactions and the production of prostaglandins via the cyclo-oxygenase pathway.[15,17] Examples of NSAIDs used in ocular allergies include ketorolac tromethamine 0.4% (Acular LS), diclofenac sodium 0.1% (Voltaren Ophtha), and nepafenac 0.1% (Nevanac; Table 5).

Ketorolac was shown to provide significant improvements in conjunctival inflammation, ocular itching, swelling, tearing, foreign body sensation, and conjunctival injection.[53] Diclofenac was shown to be as effective as ketorolac in the treatment of SAC.[66] Although topical NSAIDs have been shown to reduce the signs and symptoms of allergic conjunctivitis, the only agents approved for SAC are ketorolac (U.S. FDA) and diclofenac (U.K.).[15,17] In Canada, these NSAIDS are indicated for the postoperative management of ocular pain and inflammation, but may be considered as off-label treatment. When NSAIDs are used in the treatment of allergic conjunctivitis, they are generally used as a short-term adjunct to superior dual-activity agents, or as steroid-sparing agents. However, the most common adverse effect of this class of medications is irritation on instillation, so it is important to counsel patients on this concern in advance. While uncommon and associated with overuse, ulcerative keratitis is also a concern with the use of NSAIDs, which further limits their use.[67]

A recent study evaluated the effectiveness of combined fluorometholone 0.1% and olopatadine 0.1% against combined ketorolac 0.4% and olopatadine 0.1% and found that while itching, burning, and tearing were observed with both treatments, combined therapy with fluorometholone was more effective in relieving redness, chemosis, mucous secretions, and eyelid edema.[68]

Other immunomodulatory agents
Several other agents may be considered to treat the inflammation associated with allergic conjunctivitis. Cyclosporin emulsion (0.05% Restasis), a calcineurin inhibitor, is indicated for the treatment of moderate to moderately severe aqueous-deficient dry eye disease; however, many studies have also demonstrated its safety and efficacy in allergic conjunctivitis, and its role as a steroid-sparing agent.[69] Tacrolimus (Protopic ointment) is a calcineurin inhibitor available in Canada (0.1% or 0.03% for adults; 0.03% for children 2–15 years), and is a non-ophthalmic preparation indicated for the second-line treatment of atopic dermatitis. While no ophthalmic preparation is available in North America, the 0.1% suspension has been studied elsewhere in VKC and allergic conjunctivitis, with favourable results.[70] Tacrolimus ointment may be used carefully around the eyes in atopic dermatitis, according to protocol (twice per day for 6 weeks; continue twice per week if needed), while taking note of recommendations for age groups and duration, as well as with informed consent mindful of the risk of malignancy.

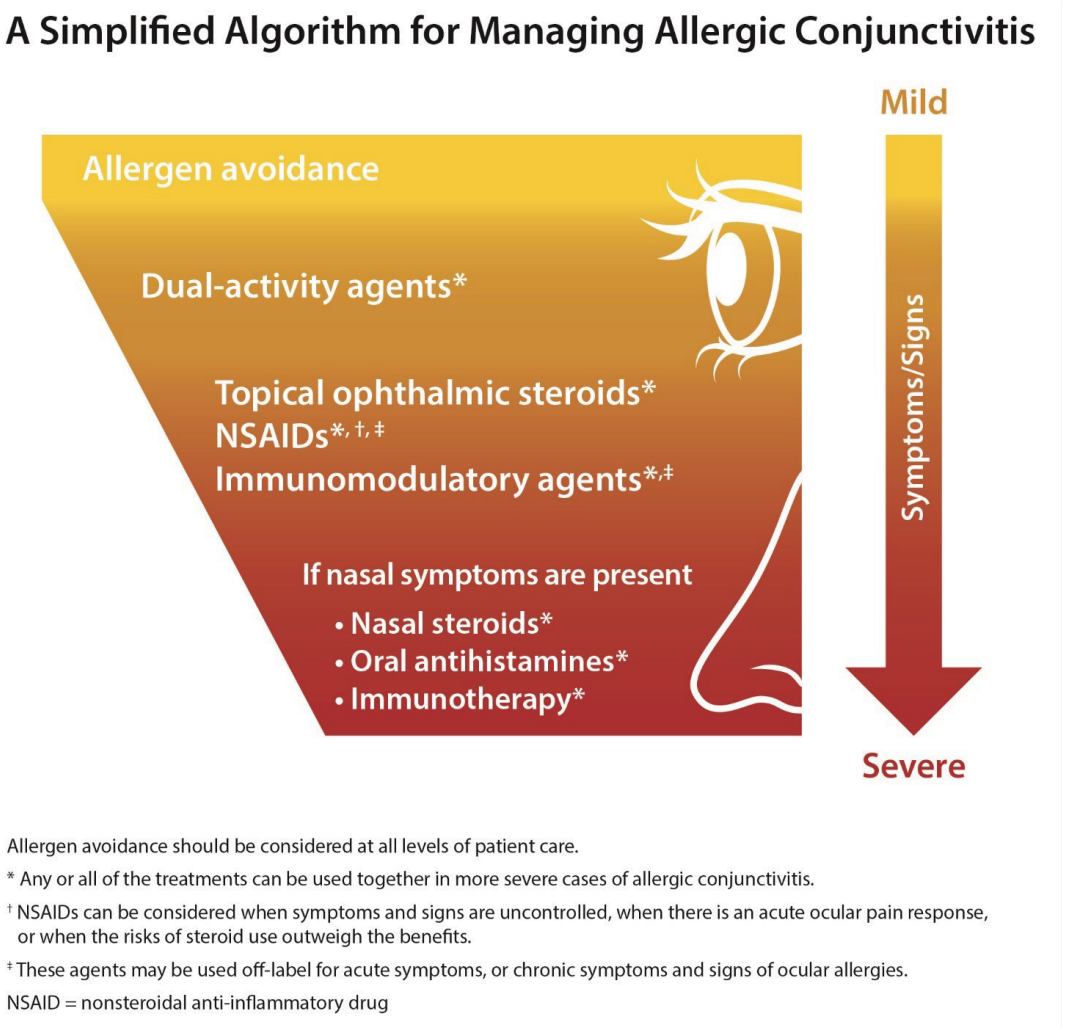
Immunotherapy
Allergen-specific immunotherapy is recommended as an important component of the management of allergic conjunctivitis and rhinitis.[71] Both subcutaneous and sublingual immunotherapy have been shown to be highly effective in the treatment of patients with severe allergic conjunctivitis, rhinoconjunctivitis, and asthma. Desensitization is achieved by exposing the patient to increasing doses of allergen over time. A three- to five-year course of treatment may lead to long-term disease-modifying benefit. Importantly, there are potential side effects to immunotherapy including anaphylaxis.

PROPOSED TREATMENT ALGORITHM FOR CANADIAN CLINICAL PRACTICE

The goal of managing ocular allergy is to provide prompt, maximal relief of symptoms and signs. The authors propose the following simplified treatment algorithm based on contemporary research and expert opinion (no consensus group was involved).

When choosing the appropriate management strategies, it is essential to examine the symptoms and signs that are present as well as their severity (refer to Tables 3 and 4), and to have an accurate diagnosis. Figure 7 provides an overview of the management strategies for allergic conjunctivitis.

Figure 7: *Management strategies for allergic conjunctivitis. NSAIDs = nonsteroidal anti-inflammatory drugs.*



Allergen avoidance is important to prevent allergic conjunctivitis; however, when avoidance fails and patients present with isolated symptoms, such as ocular itching, dual-activity agents should be prescribed first. Generally, contact lens wear will need to be discontinued or curtailed in more significant presentations, though application of a drop before insertion of contact lenses and again after removal (with twice per day medications) may be an appropriate strategy where symptoms are controlled. When symptoms become severe and signs are noted with or without the use of dual-activity agents, topical ophthalmic steroids should be considered. Further, when there is nasal involvement, the use of nasal steroids should be considered. Indeed, nasal steroids may be indicated for ocular symptoms that are refractory to topical ophthalmic treatment with or without rhinitis. If ocular and nasal symptoms are more severe, oral antihistamines should be considered. Due to adverse effects including drying of the ocular surface, the risks and benefits of these agents must be weighed in each clinical scenario. In addition, subcutaneous or sublingual immunotherapy should be considered when avoidance and medical therapy are ineffective or poorly tolerated, particularly in children.[72]

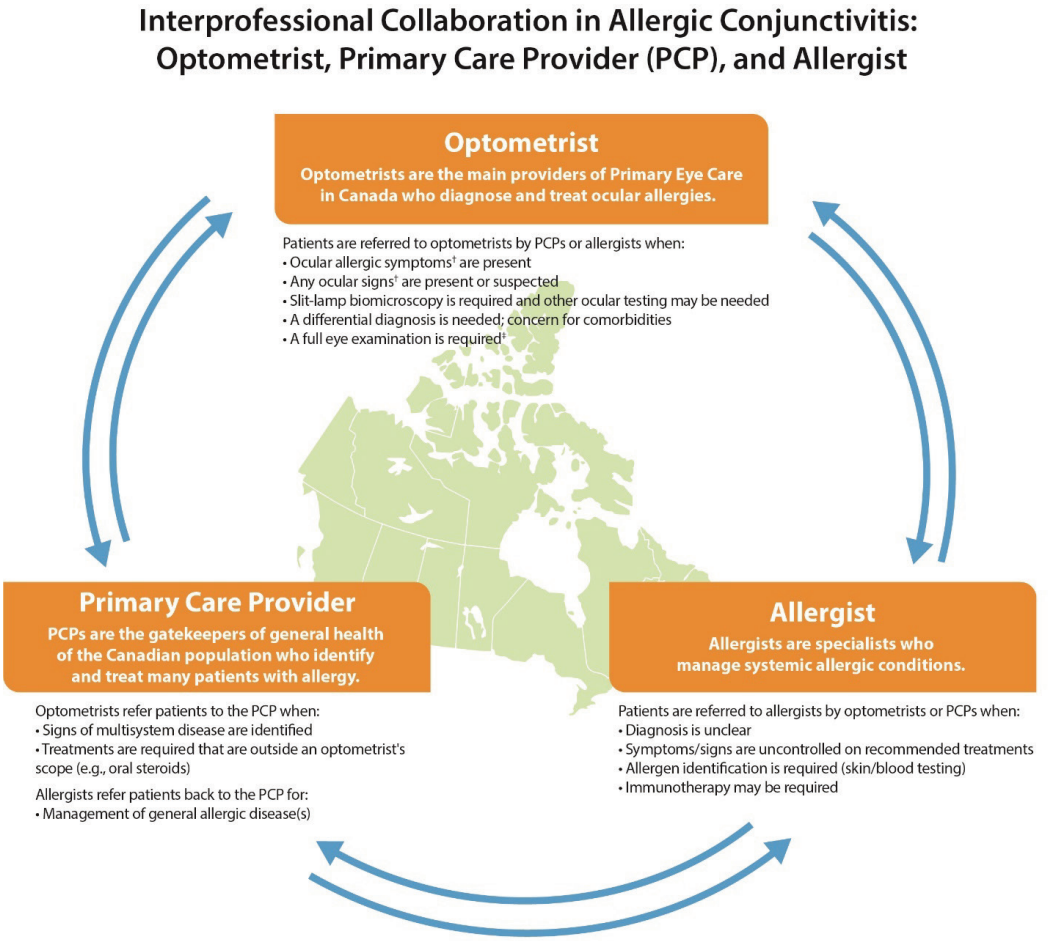
Any or all of the above treatments can be used in combination in cases of allergic conjunctivitis. Once symptoms and signs are controlled under slit-lamp biomicroscopy, steroids may be tapered or discontinued. Given the safety profile of loteprednol etabonate 0.2%, longer-term use is considered to be safe under continued evaluation using slit-lamp biomicroscopy and applanation tonometry, and tapering may not be required. In addition, NSAIDs and/

or calcineurin inhibitors (immunomodulatory agents) can be used as off-label treatments if the symptoms/signs are uncontrolled with the current medication(s).

INTERPROFESSIONAL COLLABORATION

Allergic diseases are on the rise in Canada and around the world. While several practitioners may see patients with allergy as the initial point of contact, a multidisciplinary approach is needed to maximize the treatment outcomes for patients with allergic conjunctivitis and other ocular allergic diseases. The optometrist, primary care provider, and allergist all play important roles in the management of ocular allergy. Figure 8 shows the conditions when a patient should be examined or treated by an optometrist, a primary care provider, and an allergist.

Figure 8: *Interprofessional collaboration - Conditions for patient referral to an optometrist, a primary care provider (PCP), and an allergist. PCP = primary care provider.*



* Referral to an ophthalmologist is not normally required in ocular allergic diseases but may be considered in rare, sight-threatening conditions or if treatment is outside an optometrist's scope.

† Please see Tables 3 and 4 for ocular symptoms and signs.

‡ If the patient has not had a full eye examination for >1 year.

PCP = Primary Care Provider

Although optometrists are primary eye care providers and are accessible in all provinces and territories in Canada, they may not be the first point of contact for patients who present to primary care providers, or who routinely see an allergist. Referral to the optometrist should be considered when a full eye examination has not occurred within the last year; when ocular allergy symptoms are present with acute pain; if the treating physician feels uncomfortable using topical steroids; when persistent ocular signs are noted; when slit-lamp biomicroscopy is required; when other ocular diseases are suspected; or when the diagnosis is not clear.

Both optometrists and primary care providers may refer to allergists when there are uncontrolled symptoms and/or signs, both ocular and systemic; when the allergic conjunctivitis does not respond to empiric therapy; when allergens require identification via skin/blood testing; and when immunotherapy may be required. Good communication between practitioners is essential for optimal care and overall consideration of the individual patient's management strategies.

Both optometrists and allergists may refer back to the primary care provider when signs of multisystem disease that require ongoing management are identified.

CONCLUSIONS

Ocular allergies, specifically allergic conjunctivitis, are highly prevalent conditions that are often underdiagnosed and undertreated, and can significantly affect quality of life. The diagnosis can be made based on an appropriate case history and physical examination; and a comprehensive approach should be used to manage both the ocular and systemic components of allergic disease. Numerous treatment options are available, and should be tailored to the individual's condition, while being mindful of symptom severity, physical findings, comorbidities, and other systemic manifestations of allergy. Accordingly, a multidisciplinary care approach is important for maximizing the diagnostic and therapeutic accuracy.

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CONTRIBUTORS

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CLP has received honoraria from Alcon, Allergan, Innova, Santen, and Shire for speaking and/or participation on advisory boards. HK has received honoraria from Astrazeneca, Merck, CSL, Shire, Sanofi, Kaleo, Pediapharm, Mylan, Oval, and Novartis for speaking and/or participation on advisory boards. MLP has not received any pharmaceutical grants or payments. The authors declare no conflicts of interest in this work. ●

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