Pathophysiology of Conjunctival Inflammation

Phillip L. Lieberman, MD

Possible causes of allergic conjunctival inflammation include seasonal and perennial allergic conjunctivitis, atopic keratoconjunctivitis, vernal conjunctivitis, and giant papillary conjunctivitis. The basic features of each condition suggest an immune/allergic pathogenesis.

Many features of these conditions support the role of IgE-mediated sensitivity in their production. In seasonal and perennial allergic conjunctivitis there is elevated IgE in serum and tears, eosinophil infiltration, eosinophil cellular contents in tears, allergen-specific IgE in tears, mast cell mediators in tears, and upregulated adhesion molecules.

Histopathologic findings of atopic keratoconjunctivitis are diagnostically specific and include a mixture of mast cell, eosinophil, and lymphocyte infiltration into the conjunctival epithelium. It is the ocular counterpart of atopic dermatitis. Atopic keratoconjunctivitis has a Th2 cytokine profile (primarily interleukin [IL]-4, IL-5, and IL-13). Langerhans-bearing cells have IgE on their surface, and the epithelium of the ocular surface is impaired.

In vernal conjunctivitis, there is conjunctival infiltration with eosinophils, degranulated mast cells, basophils, plasma cells, lymphocytes, and macrophages. Histopathology suggests a mixture of Th2- and Th1-driven pathology. Tear fluid contains mast cell and eosinophil mediators. About 20% to 30% of patients with this condition have phenotypically characteristic vernal conjunctivitis but are not allergic.

Giant papillary conjunctivitis is associated with the infiltration of basophils, eosinophils, plasma cells, and lymphocytes, which suggests a mixed mast cell- and lymphocyte-mediated process. There is increased messenger RNA for Th2 cytokines (IL-3, IL-4, and IL-5). There is neutrophilic chemotactic factor in tear fluid.

Complex Allergic Response in the Eye

Complex pathogenesis is involved in all of these diseases. A study comparing atopic and nonatopic subjects in which one eye in the atopic subjects was challenged, while the other eye was left unchallenged, compared to nonatopic subjects in whom one eye was challenged showed that mediators associated with allergy and mast cell degranulation were released into the tears of the challenged eye in allergic individuals but not in nonallergic individuals.1

A study of individual cellular levels in
is a growing number of patients with signs and symptoms of allergic conjunctivitis yet there is no evidence of atopy upon testing. This nonallergic conjunctivitis is quite similar to nonallergic rhinitis syndromes, such as vasomotor rhinitis. A review of the current understanding of this disease process is needed. There have been advancements in the understanding of the quality-of-life impact, pathophysiology and treatment options available for allergic conjunctivitis. By becoming more aware of the most contemporary issues in allergic conjunctivitis, practitioners in allergy and immunology settings can benefit from this important update.

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the substantia propria of bulbar conjunctival biopsy specimens 6 hours after allergen challenge in 9 atopic and 22 normal subjects revealed a broad-based inflammatory response involving CD4 cells, CD8 cells, B cells, and neutrophils.1

Upregulation of adhesion molecules occurs after allergen challenge, and drugs downregulate that expression. A study by Choi and Bielory traced mediators after a single allergen challenge.2 Some mediators were bimodal and some were not bimodal, and there was multiple mediator release.

The Importance of the Mast Cell
The mast cell is central to conjunctival inflammation.1 The majority of the mast cells in the conjunctiva are MCT cells (i.e., connective tissue mast cells). There is ingress of MCT cells during pollen season or allergen exposure. In a mast cell deletion animal model, both the early phase and late phase allergic responses to allergen exposure were blunted.4

Non-IgE Mediated Pathways
In addition to the classic IgE-mediated response, other pathways are operative.

It has been found that allergen exposure primes ocular allergic disease.

For example, upregulation of chemokine receptor 4 and chemokine receptor 5 are seen.2 In vernal conjunctivitis, there is increased chemokine receptor 46 and matrix metalloproteinases 4 and 9,7 which is unexpected. There also is upregulation of toll receptors 3, 4, and 9.7 IL-12 (i.e., T-helper-driven response) enhances the late phase response in animal models.8 Ragweed pollen causes mast degranulation via reactive oxygen species.10 Reactive oxygen species are found unrelated to the allergic response. This molecule has an innate ability to produce pathophysiology in the eye.

Surprisingly, neurokinins play a role in ocular disease. Nerve growth factor and vasoactive intestinal polypeptide enrich the pathophysiology of allergic eye disease.11 Additionally, endogenous mediators play a role in allergic ocular disease. There are downregulation symptoms associated with every pathology. The late phase response of ocular allergy is downregulated by prostaglandin E2 via the EP3 receptor. It has been found that allergen exposure primes ocular allergic disease. An eye that is challenged with allergen and subsequently given a hyperosmolar challenge will react to a greater extent than prior to challenge.12

Vasomotor conjunctivitis causes red eyes but is not an allergic condition. There is no IgE involved.

In conclusion, the immunopathogenesis of allergic eye disease is complex and involves classic IgE-mediated responses as well as Th1-driven activity and the recruitment of other pathways, especially in vernal conjunctivitis and atopic keratoconjunctivitis. The level of each is dependent on the disease involved. The inflammation is probably accompanied by endogenous downregulating activity, and it results in nonspecific hyperactivity.

Impact of Ocular Inflammation on the Patient
Michael S. Blaiss, MD

Nasal symptomatology is the hallmark of allergic rhinitis, but ocular symptoms can be just as important. In fact, historic definitions of allergic rhinitis included ocular symptoms as important components of the total symptom complex.

Allergic Conjunctivitis

Allergic conjunctivitis is more common in males under age 15 and in females over age 15. There are no differences in incidence between races. Allergic conjunctivitis improves with age, just as rhinitis does. Almost all allergic conjunctivitis patients have a family history of atopy. Eighty-eight percent of allergic conjunctivitis patients have allergic rhinitis, 17% have asthma, and 11% have atopic dermatitis.

A study by Vanna et al. in Brazil showed that 13% of 6- to 7-year-olds and 13% of 13- to 14-year-olds had ocular allergy symptoms.13 A study by Hesselmar et al. in Sweden found that 19% of 12- to 13-year-old children had eye symptoms and positive skin tests. Over half (54%) of them had taken medication for ocular allergy in the past year.14 Wüthrich et al. evaluated 509 seasonal allergy patients in primary care physician offices in Austria.15 They found that 85% had conjunctivitis symptoms. Eye symptoms predominated in 22% of patients, nasal symptoms in 25%, and both in 53%. The authors concluded that eye symptoms are at least as severe as nasal symptoms in patients with hay fever. Eye symptoms are present in almost all hay fever patients and they are clinically relevant in almost 70% of patients.

An observational, descriptive, cross-sectional study was performed on allergic patients treated by 340 allergy specialists in private and public consultations in the Spanish health system.16 Clinical, epidemiologic, diagnosis, therapeutic, social, and healthcare data were collected from 4,991 allergic patients treated for the first time in the practices of the researchers. A diagnosis of allergic rhinitis was made in 2,771 (55.5%) patients (65% had rhinoconjunctivitis and 35% had rhinitis). There were slightly more women (55%) than men (45%) in the rhinoconjunctivitis subsample.

A national cross-sectional study was conducted in Portugal to characterize clinical and demographic aspects of allergic conjunctivitis using a structured questionnaire.17 Patients were evaluated by ophthalmologists in different hospital settings. A total of 220 patients were enrolled (mean age 31.4±18.5 years). One-quarter of these patients had more than five episodes of ocular allergy in the past year, and 59.3% had year-round episodes. Most patients presented with associated comorbidities (e.g., allergic rhinitis in 45.9%, asthma in 15.5%). They had significant impairment of their overall quality of life during an acute episode. Over 45% had a score of 6 or greater on a 10-point severity scale.

Allergic conjunctivitis is more common in males under age 15 and in females over age 15.
About 20% had an appointment with an ophthalmologist as a first action and most (56.1%) started with self-treatment measures. Only 37.2% of patients had a previous evaluation for allergy.

In Juniper’s Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ), one of the major domains measured is eye symptoms, specifically itchy, watery, swollen, and sore eyes.

The Allergies in America Study, published in 2006-2007, looked at 2,500 adult Americans in all 50 states with a history of allergic rhinitis, nasal allergy, or hay fever who were symptomatic and/or on treatment. When the researchers asked about symptoms during the worst month in the past year, 25% of survey respondents reported watery eyes every day and 15% on most days. Twenty percent reported that watering eyes was extremely bothersome and 31% reported it to be moderately bothersome. Red, itching eyes was reported by 23% to be extremely bothersome and by 30% to be moderately bothersome. When asked about the most bothersome symptom of nasal allergies, 10% said red, itching eyes and 5% said watering eyes.

In the Allergies in Latin America Study, which included eight countries, 33% of survey respondents reported red or itching eyes every day or most days during the worst month in the past year. Watering eyes was also reported by 33%. Itching eyes was considered extremely bothersome by 41% of respondents and moderately bothersome by 32%. Watery eyes were considered extremely bothersome by 37% and moderately bothersome by 36%.

The Allergies in Asia-Pacific Study reported similar findings as the United States and Latin America studies. The highest rate of watering or tearing eyes during the worst month was reported in the Philippines, followed by Australia. The lowest rate was in Korea.

Questionnaires in Quality of Life with Ocular Allergy

In Juniper’s Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ), one of the major domains measured is eye symptoms, specifically itchy, watery, swollen, and sore eyes. The emotional function domain includes “embarrassed by nose or eye symptoms.”

A quality-of-life questionnaire for children with vernal keratoconjunctivitis was developed in 2007 in Italy (Questionnaire to Assess QOL in Children with VKC [QUICK]). The symptom found to be most bothersome was “burning in your eyes,” followed by “trouble staying in air-conditioned rooms,” having to use tissues, puffy eyes, problems in the light, and tearing.

Another quality-of-life measurement tool is the Eye Allergy Patient Impact Questionnaire. It looks at symptomatology and quality of life associated with ocular allergy. It asks patients to rate on a scale of 1 to 6 how often in the past week they suffered from each of the following eye allergy symptoms: swollen/puffy eyes or eyelids, watery eyes, red eyes, itchy/burning eyes, and dry eyes. The questionnaire also asks about the impact of eye allergy symptoms on activities (e.g., reading, driving, going outdoors, sleeping, concentrating on daily tasks, and putting on/wearing make-up). It also addresses emotional issues associated with eye allergy (e.g., fatigue, frustration, irritability, embarrassment, and discomfort in social and business settings). The questionnaire also asks the patient to rate their satisfaction with treatment of eye allergy symptoms.

A study by Alexander et al. helped to validate the Eye Allergy Patient Impact Questionnaire. They demonstrated a correlation between severity of eye symptoms and impact on daily life and impact on psychosocial factors.

A study from Spain looked at the quality-of-life aspects and economic consequences of seasonal allergic conjunctivitis among patients at private eye clinics. The study included 201 patients with seasonal allergic conjunctivitis diagnosed by ophthalmologists and 200 controls between 10 and 80 years of age. They used four questionnaires for these patients: EQ-5D Health Questionnaire (a generic quality-of-life questionnaire), National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) (the impact of a disease on visual functioning), RQLQ, and Health Economic and Demographic Questionnaire (HEDQ).

Compared to the control group, patients with seasonal allergic conjunctivitis had a higher rate of comorbidities, including perennial allergic conjunctivitis, nasal symptoms, asthma, food allergies, and other allergies. On the EQ-5D Health Questionnaire, poorer quality of life—as measured by factors such as mobility, self-care, ability to engage in usual activities, pain, discomfort, anxiety, and depression—was seen in patients with seasonal allergic conjunctivitis compared to controls.

On the VFQ-25, patients with seasonal allergic conjunctivitis scored statistically significantly worse than controls on distance vision, ocular pain, mental health, dependency on others, role limitations, and overall vision.

On the RQLQ patients with seasonal allergic conjunctivitis scored statistically significantly worse in all domains (e.g., activity, sleep, nose and eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional symptoms). The HEDQ questionnaire found that 20% of patients with seasonal allergic conjunctivitis missed work due to their condition, and 45% reported that they had decreased productivity of 35% (±18.58%).

Costs of Allergy

Healthcare costs are divided into direct and indirect costs. Direct costs encompass the monies spent on the course of managing the disease, including medical services (e.g., outpatient costs, physician fees, and laboratory procedures), pharmaceutical agents, and allergen immunotherapy. Indirect costs encompass all the non-healthcare costs associated with the illness. These include monies lost due to missing work and decreased productivity due to the illness. Other indirect costs include the monetary value of missing school and unpaid caregivers’ time to care for a sick child.

In the Allergies in America Study, 1,315 of the 2,500 participants were full-time workers. When they were having no symptoms, their productivity was 95%. When they experienced symptoms at their worst, productivity dropped to 72%. There was about a 20% drop in productivity related to nasal and ocular symptomatology in this survey. Looking at work interference from allergies, 10% of participants missed work, 22% reported symptoms only interfered with work, and 20% both missed work and had decreased productivity.

In conclusion, both asthma and allergic rhinitis lead to significant impairment in quality of life and increased healthcare costs. Research is clearly showing that ocular allergy worsens quality of life and adds to healthcare costs.
Current and Future Treatment Options in Allergic and Nonallergic Conjunctivitis

Leonard Bielory, MD

A new set of practice parameters for the treatment of allergic conjunctivitis have been written and are currently under review. In this document—Allergic Conjunctivitis Practice Parameters—seasonal allergic conjunctivitis and perennial allergic conjunctivitis are divided into intermittent (symptoms present less than 4 days a week or for less than 4 weeks) and persistent (symptoms present greater than 4 days a week and for greater than 4 weeks).

Treatment of allergic conjunctivitis involves a step-up approach, beginning with allergen avoidance and environmental control, followed by lubricants and cool compresses, topical antihistamines, topical agents, and immunotherapy.

Ocular Allergy Treatments

Primary treatment for both acute and chronic ocular allergy symptoms is with cool compresses and lubrication. Cold compresses decrease nerve C fiber stimulation and reduce superficial vasodilation. For patients with chronic allergy symptoms who wear contact lenses, use of disposable daily contact lenses is advised. Secondary treatment for both acute and chronic ocular allergy involves topical agents. Antihistamines can be used for pruritus. The particular agent must be carefully chosen, especially because antihistamines have anticholinergic properties and thus may cause dry eyes, which can complicate the disease. A form of dry eye called tear film dysfunction commonly occurs concurrently with ocular allergy. This may occur in a person who works long hours staring at a computer screen. The treatment is topical cyclosporine.

Decongestants are useful for erythema. Multiple action agents are recommended for evolving perennial rhinoconjunctivitis. Mast cell stabilizing agents (e.g., cromolyn) may be used for healing corneal defects associated with the more chronic forms of ocular allergy.

In general, steroids are reserved for cases of severe seasonal allergy. Steroid burst therapy may be used for 2 to 3 days. Steroids should not be used in combination with an antibiotic. If an antibiotic is needed for an infection, the steroid should be used with extra caution unless working with an ophthalmologist or other eye care professional. Topical steroids are commonly used in the treatment of chronic forms of ocular allergy, such as atopic and vernal keratoconjunctivitis.

The new practice parameters use a graded approach to pharmacotherapy for allergic conjunctivitis, involving progressive treatment in a step-wise fashion until adequate control is achieved (see Figure 1). Grade 0 is quiescent and no treatment is necessary. Grade 1 is mild intermittent. Treatment is allergen avoidance, disposable contact lenses, or oral antihistamines. Grade 2 is moderate intermittent or moderate persistent. Treatment is with daily administration of multiple action agents. Grade 3 is severe. Additional treatments may include topical cyclosporine or a short burst of topical steroids. For grade 4 (very severe) oral steroids may be added. Immunotherapy or nasal steroids are used to treat comorbidities, such as allergic rhinitis.

Secondary Treatments

Topical mast cell stabilizers include cromolyn, lodoxamide, nedocromil, and pemirolast. They require premedication. Cromolyn prevents release of mediators and is effective for allergic diseases, especially those associated with corneal changes. It relieves mild-to-moderate symptoms of vernal keratoconjunctivitis. It may be associated with burning, stinging, periorbital erythema, and chemosis. It requires dosing four times per day. Lodoxamide has in vitro anti-inflammatory properties. It is greater than 100 times more potent than cromolyn in vitro. Nedocromil is a cromolyn derivative that is effective with twice-daily dosing. It can cause yellow staining on clothing. Pemirolast is indicated for ocular pruritus and is effective when dosed twice to four times a day.

Topical antihistamines (e.g., levocabastine, emedastine) relieve signs and symptoms of pruritus (and erythema). Dosing is one to four times daily. They are safe and effective for patients 3 years old and older. Topical NSAIDs (e.g., ketorolac) relieve pruritus. Stinging and/or burning on instillation is experienced in up to 40% of patients.

Topical antihistamines and decongestant combination drugs (e.g., antazoline-naphazoline, pheniramine-naphazoline) are available without a prescription. They have quick onset of action, are more effective than systemic antihistamines, have limited duration of action, require frequent dosing, and are not recommended for regular use due to the potential for conjunctivitis medicamentosa.

There are several topical multiple action agents (antihistamine, mast cell stabilizer, cytokine), including olopatadine, ketotifen, azelastine, epinastine, and the most recently approved bepotastine and alcaftadine. They treat itch and are more effective at relieving symptoms than other classes of agents. They have longer duration of action and are safe and effect...
Advances in the Understanding and Treatment of Allergic and Nonallergic Conjunctivitis

A phase reaction in ocular allergy. Epidemiological survey in hay fever patients: symptom prevalence and severity and influence on Allergies in Childhood: validation of the rhinitis symptom questionnaire and prevalence of rhinitis in a murine model of allergic conjunctivitis. Itrelieves all facets of the inflammatory response (primarily late phase), including erythema, edema, and pruritis (not histamine induced). It is dosed four times a day and is appropriate for short-term use only. It is contraindicated in patients with viral infections. It is adjunctive therapy, although it may be considered in conjunction with allergic rhinitis and conjunctivitis. It has a contact lens with ketotifen. Preliminary results show no adverse effects. A ketotifen patch is also being studied. In addition, NSAIDs, such as topical bromfenac, are being studied for allergic conjunctivitis and potentially for tear film dysfunction (a common comorbid state with ocular allergy).

**Histamine Receptors in Ocular Tissue**

Histamine is one of the most common chemical mediators causing pruritus. In addition to histamine (specifically H1 and H4), other sensory molecules on nerves include opioids, leukotriene B4, prostat glandin E, osmosality, neurokinins, proteases, among others.

Several histamine receptors are in ocular tissue. Histamine binding to H1 receptors causes ocular itch. Stimulation of H4 receptors in blood vessels causes vasodilation. A study by Abelson and Uedel showed that instillation of a known H4 agonist (dimaprit) induced hyperemia. Onset was at 10 minutes and peak effect was at 30 minutes. There was no itch associated with H4 receptor stimulation. Itch occurs first, followed by redness. Pretreatment of the paired eye with the H4 agonist cimetidine decreased hyperemia. Pretreatment with an H4 agonist had no significant effect. H4 receptors are clinically important in the eye.

Katagiri et al. showed that eye itch will be reduced if the H4 receptor is blocked with an antagonist. Adding an H4 receptor antagonist has minimal, if any, effect.

H1- and H2-receptor antagonists have the effect of increasing itching. H4 is a novel receptor that has been shown to reduce itching, and some binding to this receptor has been noted with alcaftadine and with higher doses of the standard H1 agents.

The direct effect of histamine (H1 and H4) is vasodilation and increased permeability, and this is a commonly sought after property in several of the ophthalmic agents. H1 plus H4 antagonism has been shown in knockout mice to reduce itching. Scratching behavior was almost totally abated in experimental pruritus with H1 plus H4 antagonism. Histamine H2 receptor antagonists may have a therapeutic role in the future for relieving pruritus in patients with allergic conjunctivitis.

**Future Therapy**

New treatments under investigation include a contact lens with ketotifen. Preliminary results show no adverse effects. A ketotifen patch is also being studied. In addition, NSAIDs, such as topical bromfenac, are being studied for allergic conjunctivitis and potentially for tear film dysfunction (a common comorbid state with ocular allergy).

**Table 1: Dosing and Adverse Effects of Multiple Acting Agents**

<table>
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<tr>
<th>Manufacturer</th>
<th>MEDA</th>
<th>Allergan</th>
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<td><strong>Rx</strong></td>
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<td><strong>Dose</strong></td>
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<tr>
<td><strong>Adverse effects</strong></td>
<td>Transient sting, headache, bitter taste (&lt;1% discontinued due to adverse effects)</td>
<td>Burning, infection (URI/cold symptoms)</td>
<td>Transient sting/burn (&lt;5%), headache (7%)</td>
<td>Transient sting/burn (&lt;5%), headache (7%), fluke-like symptoms (10%)</td>
<td>Transient sting/burn (&lt;5%), headache, nasal polyposis (&lt;5%)</td>
<td>Transient sting/burn, headache, fluke-like symptoms (&lt;4%)</td>
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**References**


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Self-Assessment Test

After reading each item carefully, please select the best response (one) and enter your choice on the reverse.

1. Which of the following “allergic” eye disorders can exist in a non-IgE-mediated (nonatopic) form?
   A. Seasonal allergic conjunctivitis
   B. Atopic keratoconjunctivitis
   C. Perennial allergic conjunctivitis
   D. Vernal conjunctivitis

2. Which one of the following conditions is most commonly associated with atopic dermatitis?
   A. Seasonal allergic conjunctivitis
   B. Atopic keratoconjunctivitis
   C. Perennial allergic conjunctivitis
   D. Vernal conjunctivitis

3. Neutrophil chemotactic factor in tear fluid is most characteristic of:
   A. Seasonal allergic conjunctivitis
   B. Giant papillary conjunctivitis
   C. Perennial allergic conjunctivitis
   D. Vernal conjunctivitis

4. A 32-year-old patient is seen for evaluation of rhinoconjunctivitis which leads to trouble working as a computer programmer. You tell the patient that productivity in adult patients with rhinoconjunctivitis decreases by what percentage when symptoms are at their worst?
   A. 5%
   B. 10%
   C. 20%
   D. 40%

5. A 26-year-old mildly asthmatic woman has been treated for several years with immunotherapy for allergic rhinoconjunctivitis. She develops progressive irritation in her right eye. Her eye initially had a ropey white discharge from one eye. Her eyelids appear to be stickier when she wakes up. On examination, an opaque, yellowish mucus strand is noted on the eyelid with moderate injection of the conjunctiva. Which of the following is contraindicated?
   A. Topical mast cell stabilizer
   B. Lubricants
   C. Cold compresses
   D. Topical combined antibiotic and steroid agent

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   A. Topical mast cell stabilizing agent
   B. Lubricants
   C. Cold compresses
   D. Topical combined antibiotic and steroid agent

8. A 48-year-old woman is referred for evaluation of allergic conjunctivitis due to recent increase in ocular irritation in both eyes. She has no history of asthma or any consistent history of seasonal allergy. She has an increase in ocular symptoms of itching and grittiness with increased blinking in early winter, especially when working at the computer. Conjunctiva were mildly injected bilaterally. She has a normal response to histamine and saline with minimal reaction to grass, pollen, and mixed trees. Skin tests to indoor allergens are negative. Which of the following is most likely to improve the underlying condition?
   A. Ophthalmic mast cell stabilizer (e.g., cromolyn)
   B. Oral antihistamine
   C. Intranasal steroid
   D. An ophthalmic multiple action agent (olopatadine, epinastine, bepotastine)
   E. Ophthalmic immune modulator (i.e., cyclosporine)

9. A 27-year-old man who works as a limousine driver and is active in outdoor sports was transferred to the Mid-Atlantic region from the Upper Midwest 2.5 years ago. He presents with intermittent respiratory symptoms previously treated with over-the-counter medication. However, drowsiness from the drugs disrupts his work. Symptoms include nasal discharge, intermittent sneezing, itching of the nose, and tearing of the eyes. He also experiences fatigue and lack of concentration while driving. Physical examination reveals swollen and pale nasal turbinates bilaterally, moderate edema and darkened suborbital regions. Allergy tests reveal large reactions to grass, weed, and tree pollen and moderate reactions to dust mite allergens. What is the best long-term treatment?
   A. Ophthalmic mast cell stabilizer (e.g., cromolyn)
   B. Immunotherapy (aeroallergens and perennial allergens)
   C. Short burst of an ophthalmic steroid
   D. Ophthalmic multiple action agent (olopatadine, epinastine, bepotastine)

10. Antagonism of H1 plus ____ has been shown in knockout mice to reduce itching.
   A. H2
   B. H3
   C. H4
   D. Leukotriene B4

Continued on reverse.
## Activity Evaluation

1. As a result of this activity, do you intend to do anything differently in your practice?  ○ Yes  ○ No

   **If Yes, what specifically?**

   **If No, what might be barriers to making any changes?**

2. Based on educational needs, please provide healthcare or professional practice gaps that should be addressed in future educational activities and that may be applicable to your practice:

3. Was this a fair and balanced publication?  ○ Yes  ○ No

   **If No, please comment on the scientific rigor, fairness, and balance of the material.**

4. Did this publication properly disclose relevant financial relationships of all persons in control of content?  ○ Yes  ○ No

   **If No, please explain:**

5. Did this publication include proper disclosure of discussion of off-label (investigational/experimental) use of medications or medical devices?  ○ Yes  ○ No

   **If No, please comment:**

6. How well organized was the publication? (1=poor, 2=fair, 3=good, 4=excellent) ________

7. How would you rate the clarity of this publication? (1=poor, 2=fair, 3=good, 4=excellent) ________

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**Answer Sheet**

Please place one answer for each test question in the appropriate box.

| 1. | 2. | 3. | 4. | 5. | 6. | 7. | 8. | 9. | 10. |
---|---|---|---|---|---|---|---|---|---|

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