ALEXEI GONZALEZ-ESTRADA, MD
Assistant Professor, Department of Internal Medicine, Quillen College of Medicine, East Tennessee State University, Johnson City

LISANNE P. NEWTON, MD
Department of Allergy and Immunology, Pediatric Institute, Cleveland Clinic

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Does allergic conjunctivitis always require prescription eyedrops?

A: No, not all patients with allergic conjunctivitis need prescription eyedrops.

For mild symptoms, basic nonpharmacologic eye care often suffices. Advise the patient to avoid rubbing the eyes, to use artificial tears as needed, to apply cold compresses, to limit or temporarily discontinue contact lens wear, and to avoid exposure to known allergens.

Topical therapy with an over-the-counter eyedrop that combines an antihistamine and a mast cell stabilizer is another first-line measure.

Prescription eyedrops are usually reserved for patients who have persistent bothersome symptoms despite use of over-the-counter eyedrops. Also, some patients have difficulty with the regimens for over-the-counter eyedrops, since most must be applied two to four times per day. In addition, patients with concomitant allergic rhinitis may benefit from an intranasal corticosteroid.

For most patients, basic eye care measures are sufficient

ALLERGIC CONJUNCTIVITIS: A BRIEF OVERVIEW

Allergic conjunctivitis, caused by exposure of the eye to airborne allergens, affects up to 40% of the US population, predominantly young adults.[1] Bilateral pruritus is the chief symptom. The absence of pruritus should prompt consideration of a more serious eye condition.

Other common symptoms of allergic conjunctivitis include redness, tearing (a clear, watery discharge), eyelid edema, burning, and mild photophobia. Some patients may have infraorbital edema and darkening around the eye, dubbed an "allergic shiner."[1]

Allergic conjunctivitis can be acute, with sudden onset of symptoms upon exposure to an isolated allergen. It can be seasonal, from exposure to pollen and with a more gradual onset. It can also be perennial, from year-round exposure to indoor allergens such as animal dander, dust mites, and mold.

Allergic conjunctivitis often occurs together with allergic rhinitis, which is also caused by exposure to aeroallergens and is characterized by nasal congestion, pruritus, rhinorrhea (anterior and posterior), and sneezing.[2]

Pollen is more commonly associated with rhinoconjunctivitis, whereas dust mite allergy is more likely to cause rhinitis alone.

An immunoglobulin E-mediated reaction

Allergic conjunctivitis is a type I immunoglobulin E-mediated immediate hypersensitivity reaction. In the early phase, ie, within minutes of allergen exposure, previously sensitized mast cells are exposed to an allergen, causing degranulation and release of inflammatory mediators, primarily histamine. The late phase, ie, 6 to 10 hours after the initial exposure, involves an influx of inflammatory cells such as eosinophils, basophils, and neutrophils.[3]

Differential diagnosis

The differential diagnosis of allergic conjunctivitis includes infectious conjunctivitis, chronic dry eye, preservative toxicity, giant papillary conjunctivitis, atopic keratoconjunctivitis, and vernal keratoconjunctivitis.[3] Giant papillary conjunctivitis is an inflammatory reaction to a foreign substance, such as a contact lens. Atopic keratoconjunctivitis and vernal keratoconjunctivitis can be vision-threatening and require referral to an ophthalmologist. Atopic keratoconjunctivitis is associated with eczematous lesions of the lids and skin, and vernal keratoconjunctivitis involves chronic inflammation of the palpebral conjunctivae. Warning signs include photophobia, pain, abnormal find-

doi:10.3949/ccjm.82a.14162

TABLE 1

Eyedrops for allergic conjunctivitis

	Dose	Over the counter?	Estimated cost[a]
Topical antihistamine			
Emedastine difumarate (Emadine) 5 mL	1 drop every 6 hours	No	$124
Mast-cell stabilizers			
Cromolyn sodium (Crolom, Opticrom) 10 mL	1 drop every 6 hours	Yes	$38–$51
Lodoxamide tromethamine (Alomide) 10 mL	1 drop every 6 hours	No	$141
Nedocromil sodium (Alocril) 5 mL	1–2 drops every 12 hours	No	$152
Pemirolast (Alamast) 10 mL	1–2 drops every 6 hours	No	$119
Combination topical antihistamine and mast-cell stabilizer eyedrops			
Alcaftadine (Lastacaft) 3 mL	1 drop daily	No	$149
Azelastine HCl 0.05% (Optivar) 6 mL	1 drop every 12 hours	No	$43
Bepostastine besilate (Bepreve) 5 mL	1 drop every 12 hours	No	$173
Epinastine HCl (Elestat) 5 mL	1 drop every 12 hours	No	$61
Ketotifen 0.025% (Alaway 10 mL, Zaditor 5 mL)	1 drop every 12 hours	Yes	$15–$70
Olopatadine HCl 0.1% (Patanol) 5 mL	1 drop every 6–8 hours	No	$212
Olopatadine HCl 0.2% (Pataday) 2.5 mL	1 drop daily	No	$156

[a] Estimated costs, August 2015, Cleveland, OH.

ings on pupillary examination, blurred vision (unrelated to excessively watery eyes), unilateral eye complaints, and ciliary flush.[2]

Bacterial conjunctivitis is highly contagious and usually presents with hyperemia, "stuck eye" upon awakening, and thick, purulent discharge. It is usually unilateral. Symptoms include burning, foreign-body sensation, and discomfort rather than pruritus. Patients with allergic conjunctivitis may have concomitant bacterial conjunctivitis and so require a topical antibiotic as well as treatment for allergic conjunctivitis.

Viral conjunctivitis usually affects one eye, is self-limited, and typically presents with other symptoms of a viral syndrome.

MANAGEMENT OPTIONS

Management of allergic conjunctivitis consists of basic eye care, avoidance of allergy triggers, and over-the-counter and prescription topical and systemic therapies, as well as allergen immunotherapy.[3]

Avoidance

Triggers for the allergic reaction, such as pollen, can be identified with aeroallergen skin testing by an allergist. But simple avoidance measures are helpful, such as closing windows, using air conditioning, limiting exposure to the outdoors when pollen counts are high, wearing sunglasses, showering before bedtime, avoiding exposure to animal dander, and using zippered casings for bedding to minimize exposure to dust mites.[3]

Patients who wear contact lenses should reduce or discontinue their use, as allergens adhere to contact lens surfaces.

Topical therapies

If avoidance is not feasible or if symptoms persist despite avoidance measures, patients should be started on eyedrops.

Eyedrops for allergic conjunctivitis are classified by mechanism of action: topical antihistamines, mast-cell stabilizers, and combination preparations of antihistamine and mast-cell stabilizer (**Table 1**). Algorithms for

Tailor treatment to symptoms, allergen profile, and patient preferences

TABLE 2

Three steps to treating allergic conjunctivitis

Step 1
Avoid allergens (guided by allergy testing, if available)
Avoid rubbing the eyes
Use artificial tears
Limit contact lens use
Apply cold compresses

Step 2
Continue **Step 1** recommendations
Over-the-counter eyedrops
(combination antihistamine and mast-cell stabilizer)
Intranasal corticosteroid for concomitant allergic rhinitis

Step 3
Prescription eyedrops
(combination antihistamine and mast-cell stabilizer)
Intranasal corticosteroid for concomitant allergic rhinitis
Consider referral [a]
Consider allergen immunotherapy [b]
Consider a short course of an oral corticosteroid if symptoms are severe, acute, or persistent

[a] Consider referral to an allergist at any step to identify allergic triggers, including relevant pollens for timing of medications before season onset; see text for differential diagnosis and red flags that should prompt a referral to an ophthalmologist; topical corticosteroid eye drops should only be prescribed with close follow-up with an ophthalmologist.
[b] For refractory cases or cases in which medications have undesirable side effects, are limited by adherence, or are undesired; allergen immunotherapy is the only disease-modifying treatment available; not indicated for acute relief of symptoms.

managing allergic conjunctivitis exist[2] but are based on expert consensus, since there are no randomized clinical trials with head-to-head comparisons of topical agents for allergic conjunctivitis.

In our practice, we use a three-step approach to treat allergic conjunctivitis (**Table 2**). Combination antihistamine and mast-cell stabilizer eyedrops are the first line, used as needed, daily, seasonally, or year-round, based on the patient's symptoms and allergen profile. Antihistamine or combination eyedrops are preferred as they have a faster onset of action than mast-cell stabilizers alone,[3] which have an onset of action of 3 to 5 days. The combination drops provide an effect on the late-phase response and a longer duration of action.

Currently, the only over-the-counter eyedrops for allergic conjunctivitis are cromolyn (a mast-cell stabilizer) and ketotifen 0.025% (a combination antihistamine and mast-cell stabilizer). Most drops for allergic conjunctivitis are taken two to four times a day. Two once-daily eyedrop formulations for allergic conjunctivitis—available only by prescription—are olopatadine 0.2% and alcaftadine. However, these are very expensive (**Table 1**) and so may not be an appropriate choice for some patients. On the other hand, a study from the United Kingdom[4] found that patients using olopatadine made fewer visits to their general practitioner than patients using cromolyn, resulting in lower overall cost of healthcare. Results of studies of patient preferences and efficacy of olopatadine 0.1% (twice-daily preparation) vs ketotifen 0.025% are mixed,[5–8] and no study has compared olopatadine 0.2% (once-daily preparation) with over-the-counter ketotifen.

Adverse effects of eyedrops

Common adverse effects include stinging and burning immediately after use; this effect may be reduced by keeping the eyedrops in the refrigerator. Patients who wear contact lenses should remove them before using eyedrops for allergic conjunctivitis, and wait at least 10 minutes to replace them if the eye is no longer red.[2] Antihistamine drops are contraindicated in patients at risk for angle-closure glaucoma.

Whenever possible, patients with seasonal allergic conjunctivitis should begin treatment 2 to 4 weeks before the relevant pollen season, as guided by the patient's experience in past seasons or by the results of aeroallergen skin testing. This modifies the "priming" effect, in which the amount of allergen required to induce an immediate allergic response decreases with repeated exposure to the allergen.

OTHER TREATMENT OPTIONS

Vasoconstrictor or decongestant eyedrops are indicated to relieve eye redness but have little or no effect on pruritus, and prolonged use may lead to rebound hyperemia. Thus, they are not generally recommended for long-term treatment of allergic conjunctivitis.[3] Also, patients with glaucoma should be advised against long-term use of over-the-counter vasoconstrictor eyedrops.

Corticosteroid eyedrops are reserved for refractory and severe cases. Their use requires close follow-up with an ophthalmologist to monitor for complications such as increased intraocular pressure, infection, and cataracts.[2]

Patients presenting with an acute severe episode of allergic conjunctivitis that has not responded to oral antihistamines or combination eyedrops may be treated with a short course of an oral corticosteroid, if the benefit outweighs the risk in that patient.

Oral antihistamines are generally less effective than topical ophthalmic agents in relieving ocular allergy symptoms and have a slower onset of action.[2] They are useful in patients who have an aversion to instilling eyedrops on a regular basis or who wear contact lenses.

For patients who have associated allergic rhinitis—ie, most patients with allergic conjunctivitis—intranasal corticosteroids and intranasal antihistamines are the most effective treatments for rhinitis and are also effective for allergic conjunctivitis. Monotherapy with an intranasal medication may provide sufficient relief of conjunctivitis symptoms or allow ocular medications to be used on a less frequent basis.

Allergen immunotherapy

Referral to an allergist for consideration of allergen immunotherapy is an option when avoidance measures are ineffective or unfeasible, when first-line treatments are ineffective, and when the patient does not wish to use medications.

Allergen immunotherapy is the only disease-modifying therapy available for allergic conjunctivitis. Two forms are available: traditional subcutaneous immunotherapy, and sublingual tablet immunotherapy, recently approved by the US Food and Drug Administration.[9] Subcutaneous immunotherapy targets specific aeroallergens for patients allergic to multiple allergens. The new sublingual immunotherapy tablets target only grass pollen and ragweed pollen.[9] Most patients in the United States are polysensitized.[10] Both forms of immunotherapy can result in sustained effectiveness following discontinuation. Sublingual therapy may be administered year-round, before allergy season, or during allergy season (depending on the type of allergy).

TAILORING TREATMENT

We recommend a case-by-case approach to the management of patients with allergic conjunctivitis, tailoring treatment to the patient's symptoms, allergen profile, and personal preferences.

For example, if adherence is a challenge we recommend a once-daily combination eyedrop (olopatadine 0.2%, or alcaftadine). If cost is a barrier, we recommend the combination over-the-counter drop (ketotifen).

Medications may be used during allergy season or year-round depending on the patient's symptom and allergen profile. Patients whose symptoms are not relieved with these measures should be referred to an allergist for further evaluation and management, or to an ophthalmologist to monitor for complications of topical steroid use and other warning signs, as discussed earlier, or to weigh in on the differential diagnosis.

REFERENCES

1. **Bielory L, Friedlaender MH**. Allergic conjunctivitis. Immunol Allergy Clin North Am 2008; 28:43–58.
2. **Bielory L, Meltzer EO, Nichols KK, Melton R, Thomas RK, Bartlett JD**. An algorithm for the management of allergic conjunctivitis. Allergy Asthma Proc 2013; 34:408–420.
3. **Wallace DV, Dykewicz MS, Bernstein DI, et al; Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology**. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008; 122(suppl 2):S1–S84.
4. **Guest JF, Clegg JP, Smith AF**. Health economic impact of olopatadine compared to branded and generic sodium cromoglycate in the treatment of seasonal allergic conjunctivitis in the UK. Curr Med Res Opin 2006; 22:1777–1785.
5. **Leonardi A, Zafirakis P**. Efficacy and comfort of olopatadine versus ketotifen ophthalmic solutions: a double-masked, environmental study of patient preference. Curr Med Res Opin 2004; 20:1167–1173.
6. **Ganz M, Koll E, Gausche J, Detjen P, Orfan N**. Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. Adv Ther 2003; 20:79–91.
7. **Aguilar AJ**. Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. Acta Ophthalmol Scand Suppl 2000; 230:52–55.
8. **Artal MN, Luna JD, Discepola M**. A forced choice comfort study of olopatadine hydrochloride 0.1% versus ketotifen fumarate 0.05%. Acta Ophthalmol Scand Suppl 2000; 230:64–65.
9. **Cox L**. Sublingual immunotherapy for aeroallergens: status in the United States. Allergy Asthma Proc 2014; 35:34–42.
10. **Salo PM, Arbes SJ Jr, Jaramillo R, et al**. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol 2014; 134:350–359.

***ADDRESS**: Lisanne P. Newton, MD, Department of Allergy and Clinical Immunology, Respiratory Institute, A120, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: newtonl@ccf.org*