

Allergic Eye Disease

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KEYWORDS

• Allergy • Conjunctivitis • Vernal • Atopic • Seasonal • Perennial

KEY POINTS

- Allergic eye disease is almost always bilateral, and itching is the predominant symptom.
- Allergic eye disease can be clinically and pathophysiologically classified as seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, contact blepharoconjunctivitis, and giant papillary conjunctivitis.
- The first step in management is avoidance of allergen and cessation of eye rubbing.
- For mild cases without evidence of corneal involvement, treatment with a combination of topical antihistamines mast cell stabilizers is highly effective, and topical nonsteroidal anti-inflammatory drugs and steroids should be prescribed by an ophthalmologist.
- The presence of pain, visual impairment, or evidence of corneal involvement should prompt referral to an ophthalmologist for further management.

INTRODUCTION

Ocular allergy, affecting approximately 10% to 20% of the US population, is one of the most common ocular disorders encountered by pediatricians and ophthalmologists.^{1,2} Patients with ocular allergy often present with bilateral inflammation of the eyelid and conjunctiva that may be associated with rhinitis, asthma, or other atopic conditions. Allergic eye disease is classified into seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), contact blepharoconjunctivitis, and giant papillary conjunctivitis (**Table 1**). The predominant symptom is itching and redness, and mucinous discharge or photophobia may be present. If pain is present, vision is impaired, the cornea is involved, or symptoms do not improve with treatment, the clinician should refer the patient to an ophthalmologist. A basic understanding of eye surface anatomy is required to fully appreciate key diagnostic elements. Initial treatment involves a combination of topical antihistamines and mast cell stabilizers. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) and occasionally short-term use of topical steroids should be prescribed ideally by an ophthalmologist, because

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Table 1
Clinical presentation and characteristics of ocular allergy

Characteristic	SAC	PAC	VKC	AKC	CBC	GPC
Age	All ages	All ages	<20 y (male>female)	Adulthood (male>female)	All ages	All ages
Onset	Childhood	Childhood	Preadolescence	Any age	Any age	Any age
Allergens	Tree pollens (early spring) Weed pollen (August–October) Outdoor molds Grasses (May–July)	Dust mites Animal dander Mold Air pollutants	Seasonal allergens	Any can contribute	Cosmetics Ophthalmic eye drops Inert chemicals	Foreign body Contact lenses Suture material Prosthesis
Seasonal	Yes	No	Yes	No	No	No
Personal or family history of atopy	Common	Common	Possible	Always	Possible	Possible
Contact lens wear	No	No	No	No	Possible	Yes
Symptoms	Itching Tearing Photophobia	Itching Tearing Photophobia	Itching Copious mucous Photophobia	Itching Burning Photophobia	Itching Burning Photophobia	Itching Tearing Photophobia
Pathophysiology	IgE-mediated Type I hypersensitivity	IgE-mediated Type I hypersensitivity	IgE-mediated Type I and IV hypersensitivity	IgE-mediated Type I and IV hypersensitivity	Type IV hypersensitivity	IgE-mediated Type I and IV hypersensitivity
Conjunctival eosinophilia	Yes	Yes	Always	Always (acute phase)	Occasional	Rare
Serum IgE	Mildly elevated	Mildly elevated	Elevated	Elevated	Variable	Variable
Goblet cells	Elevated	Elevated	Marked elevation	Decreased	Variable	Variable
Periocular skin involvement	Sometimes edema	Sometimes edema	Sometimes edema	Sometimes edema, sometimes eczema	Dermatitis, sometimes edema	Sometimes edema
Visual impairment	+/-	+/-	++	+++	+/-	+/-

Conjunctival reaction	Papillary	Papillary	Giant papillary reaction (upper tarsus)	Papillary reaction/thickened (upper tarsus)	Papillary or follicular response	Giant papillary reaction
Corneal involvement	+/-	+/-	++	++++	+	+
Skin tests	Positive	Positive	Positive	Positive	Variable	Variable
Natural history	Self-limited; symptomatic treatment	Self-limited; symptomatic treatment	Requires treatment; usually resolves by age 20 y	Chronic	Short-term; requires treatment	Chronic; contact lens associated
Concurrent ocular complications	None	None	Shield ulcer (sterile ulcer)	Cataracts Secondary infections (HSV, staphylococcal) Glaucoma	None	Peripheral corneal pannus
First-line prophylaxis	Avoidance Mast cell stabilizers	Avoidance Mast cell stabilizers	Mast cell stabilizers	Avoidance Mast cell stabilizers	Avoidance	Avoidance Mast cell stabilizers
First-line acute treatment	Topical antihistamine/ mast cell stabilizers	Topical antihistamine/ mast cell stabilizers	Should be treated by ophthalmologist Topical antihistamine/ mast cell stabilizers Topical cyclosporine Topical mild steroid Allergist referral Possible systemic treatment Topical corticosteroid pulse	Should be treated by ophthalmologist Topical antihistamine/ mast cell stabilizers Topical cyclosporine Topical mild steroid Allergist referral Possible systemic treatment May require chronic treatment Topical corticosteroid pulse	Mild topical corticosteroid to periocular skin	Topical antihistamine/ mast cell stabilizers

Abbreviations: CBC, contact blepharoconjunctivitis; GPC, giant papillary conjunctivitis; HSV, herpes simplex virus; PAC, perenneal allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; VKC, vernal keratoconjunctivitis; +/-, may or may not be present; +, sometimes present; ++, usually present; +++, often present; +++++, always present.

both medications can have complications that are difficult to recognize without a detailed ophthalmic examination.

CLASSIFICATION

Seasonal Allergic Conjunctivitis

Epidemiology and risk factors

Seasonal allergic conjunctivitis (“hay fever” conjunctivitis), representing 25% to 50% of cases of ocular allergy, is the most common allergic disease of the eye.³ SAC is associated with hypersensitivity to airborne allergens, such as tree pollens (early spring), weed pollen (August through October), outside molds, grasses (May through July), or other environmental antigens depending on geographic distribution. Seasonal allergic conjunctivitis is most severe during the spring, summer, and early fall when the pollen levels are high.

Pathophysiology

Seasonal allergic conjunctivitis is classically a type I hypersensitivity reaction, caused by the binding of environmental airborne allergens such as pollen to IgE receptors in mast cells, which leads to degranulation of mast cells of the MC_T subtype. The release of proinflammatory mediators attracts eosinophils and basophils.

Clinical presentation

Seasonal allergic conjunctivitis is bilateral, with acute or subacute onset and peaks corresponding to seasonal variation in airborne antigens. Itching is the predominant symptom, although tearing, photophobia, and a burning sensation may be present. The eyelids and conjunctiva are typically involved. Conjunctival involvement may present as chemosis (swelling) and injection (redness), with chemosis more impressive than injection in most cases. Corneal involvement is rare, but mild punctate epithelial keratitis (small dry spots on cornea) may be present.

Perennial Allergic Conjunctivitis

Epidemiology and risk factors

Perennial allergic conjunctivitis has a similar clinical presentation to SAC, although usually milder. However, the allergens are often indoor antigens, such as dust mites, animal dander, and molds. Therefore, a definitive seasonal distribution is not uniformly present. The condition can be associated with dry eye syndrome, which is often undiagnosed in the pediatric population.⁴

Pathophysiology

Like SAC, PAC is IgE-mediated mast cell degranulation (MC_T) of proinflammatory mediators with recruitment of eosinophils.

Clinical presentation

Patients with PAC present with milder disease than those with SAC, and itching is the predominant symptom. Chemosis is often more impressive than conjunctival injection, but both tend to be present. A fine papillary reaction is present on the palpebral conjunctiva (**Fig. 1**). Dry eye syndrome may exacerbate the condition and requires separate treatment. Corneal involvement is rare in PAC alone and is usually only identified in cases of simultaneous PAC and dry eye syndrome.

Vernal Keratoconjunctivitis

Epidemiology and risk factors

Vernal keratoconjunctivitis represents 0.5% of allergic ocular disease.⁵ Vernal keratoconjunctivitis affects mainly children and young adolescents ages 11 to 13 years, with



Fig. 1. Fine papillary reaction of the superior tarsal conjunctiva in PAC. (Courtesy of A. Kaufman, MD, Cincinnati, OH.)

a male predominance.⁵ Both genetic and environmental factors likely play a role in the disease process. Approximately 50% of patients will have a history of atopy, such as asthma, allergic rhinitis, or eczema. Vernal keratoconjunctivitis is more common in hot and dry climates.

Pathophysiology

Although the precise pathophysiology is unknown, both type I and IV hypersensitivity reactions contribute to the pathogenesis,⁶ with antigenic stimulation leading to lymphocyte (mainly T-helper type 2 [Th2] cells) activation with intense eosinophilic infiltrate. In addition, goblet cells are increased with elevation of mucin-5AC (MUC5AC) levels, and subsequent abundant mucous is observed with this condition.⁷

Clinical features

Bilateral, intense itching is the predominant symptom of this condition, often accompanied by photophobia and ropey discharge. Two anatomic forms exist: (1) palpebral, with giant upper tarsal papillae (>1 mm, often 7–8 mm), giving a “cobblestone” appearance on the surface of an everted eyelid ([Fig. 2](#)), and (2) limbal bulbar conjunctiva, which create gelatinous eosinophilic mounds (known as *Trantas dots*) at the limbus ([Fig. 3](#)). Both of these findings can be identified without ophthalmologic



Fig. 2. Giant papillae of the superior palpebral conjunctiva in a patient with vernal conjunctivitis. (Courtesy of A. Kaufman, MD, Cincinnati, OH.)

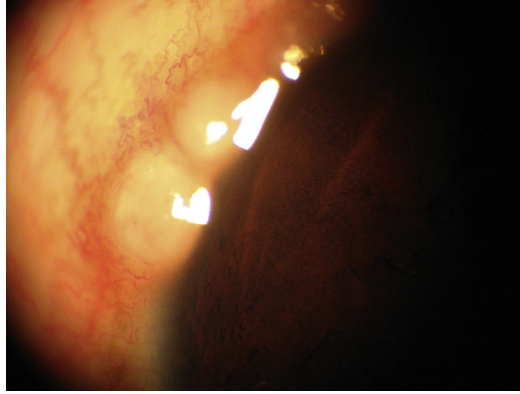


Fig. 3. Horner trantas dots in the limbal subtype of vernal conjunctivitis. (Courtesy of D. Saltarelli, OD, Cincinnati, OH.)

magnification. Eyelid edema is concurrent with conjunctival injection. Importantly, 5% of patients will have corneal involvement,⁸ which can lead to visual impairment. If not treated, corneal involvement can eventually lead to permanent scarring. The giant papillae on the upper tarsal surface can cause mechanical trauma or “rubbing” of the cornea. A slit lamp examination is required to identify the following findings:

- Superficial punctate keratopathy: small pinpoint areas of fluorescein uptake on the upper half of the cornea
- Corneal macroerosions and/or shield ulcers: sterile infiltrate with overlying epithelial loss leading to intensely staining patch on the upper half of the cornea
- Superficial pannus formation and opacification of the cornea adjacent to the superior limbus

Decreased vision or suspicion for corneal involvement should prompt semiurgent referral to an ophthalmologist for further evaluation.

Atopic Keratoconjunctivitis

Epidemiology and risk factors

Atopic keratoconjunctivitis is a severe, chronic inflammatory disorder that is more common in adult patients aged 20 to 50 years, with a male predominance.⁹ Some patients can present at a very young age. Personal and family histories are significant for atopic disease in 95% of patients, with atopic dermatitis the most common associated disorder.¹⁰

Pathophysiology

The immunopathology is complex, with both type I and IV hypersensitivity reactions contributing to the condition. Unlike with VKC, there is a reduction in MUC5AC-secreting goblet cells.

Clinical features

Symptoms of AKC include itching, burning, tearing, and erythematous/swollen eyelids. The eyelids have an eczematous appearance and there may be madarosis (loss of eyelashes) from scratching. The chronic eyelid edema produces a classic Dennie-Morgan fold in the lower eyelid or an “allergic shiner.”

Unlike VKC, the inferior tarsal conjunctiva is more likely to be involved with smaller (<1 mm) papillae. Chronic inflammation can lead to adhesions (symblepharon) within the lower fornix. Corneal complications are present in many patients with this disorder, and may include punctate epithelial keratitis (most prominent in the lower cornea), pannus formation, and frank ulceration. Patients with AKC have an increased susceptibility to herpetic keratitis, which can be severe and vision-threatening.

Contact Blepharoconjunctivitis

Epidemiology and risk factors

Contact blepharoconjunctivitis is secondary to re-exposure to cosmetics, chemicals, and some household plants (Table 2). Patients with and without atopy are affected.

Pathophysiology

Contact blepharoconjunctivitis is a type IV hypersensitivity response in which the allergen serves as a hapten (incomplete antigen) and combines with other proteins to form an immunologically active antigen. Langerhans cells, which are type 2 major histocompatibility complex antigen-presenting cells, present antigens to T-helper type 1 (Th1) cells in the regional lymph nodes. The sensitization phase develops over weeks to months, and the sensitized T cells migrate to the ocular surface and release cytokines and promote chemotaxis of other inflammatory cells. Unlike in SAC and PAC, in which inflammation occurs within 2 to 3 hours, the reaction to the offending agent takes 48 to 72 hours. This reaction should be differentiated from those to toxic or mechanically irritative substances, which manifest within 2 to 3 hours.

Clinical features

Contact blepharoconjunctivitis is characterized by symptoms of itching and burning. The conjunctiva is usually involved, and the eyelid has an acute eczematous,

Table 2
Common products associated with contact blepharoconjunctivitis

Class	Examples
Cosmetics	Nail varnish Eyeliner Mascara (often contain nickel) Soaps
Preservatives	Benzalkonium chloride (found in many topical ophthalmic solutions) Thimerosal (contact lens solutions)
Antimicrobial agents	Polymyxin Aminoglycosides Sulfonamides Trifluridine
Other ophthalmic medications	Atropine Homatropine Tropicamide Scopolamine Tetracaine Dorzolamide

erythematous appearance. The chronic phase leads to lichenification of the eyelid skin. The conjunctiva may have a papillary or follicular appearance. The lower cornea may demonstrate superficial punctate keratitis, usually in the lower half where the offending substance pools.

Giant Papillary Conjunctivitis

Epidemiology and risk factors

Giant papillary conjunctivitis most commonly presents in contact lens wearers. Patients with history of atopy are at higher risk, and materials such as contact lenses, ocular prostheses, suture material, or foreign bodies are often the inciting elements.

Pathophysiology

Mechanical trauma of the conjunctival epithelium stimulates a Th2 lymphocyte-mediated response. An allergic component may be involved when protein deposits on contact lenses or prostheses serving as allergens create a type I hypersensitivity response. Alternatively, protein deposits can serve as haptens and create a type IV hypersensitivity response in some cases.

Clinical features

The foreign body or contact lens may be present for months to years before symptoms occur. Symptoms consist of intense itching, mucous discharge, and photophobia. Giant papillae (>1 mm) are usually present on the tarsal surface adjacent to the foreign body. Removal of the foreign body, cessation of contact lens use, or change to other types of contact lens can alleviate symptoms.

CLINICAL ASSESSMENT

History

The history should include onset, duration, exacerbating factors, relieving factors, and previous episodes, with attention to seasonal variation. Current or prior treatments including duration and previous compliance should be evaluated. Personal or family history of atopy (asthma, eczema, or allergic rhinitis) should be evaluated. One should inquire about new pets, recent relocations, remodeling projects, or other household exposures. The predominant symptom is itching and the condition is usually bilateral (it can be asymmetric). Complaints of significant pain or blurring of vision unrelated to tearing should alert the clinician to alternative causes. The clinician should ask whether the patient had recent contact with anyone with conjunctivitis to rule out a possible infectious origin.

Examination

Examination should include evaluation of the body for other skin lesions (eczema) or mucous membrane involvement. The examination should also include palpation for preauricular or submandibular and cervical lymphadenopathy, because these findings would be more consistent with an infectious origin. Monocular best-corrected visual acuity (with the child in glasses if these are worn) should be measured with a near card or at a distance. Pupils should be examined for any evidence of afferent pupillary defect or asymmetry. Extraocular movements should be assessed. The eyelid skin should be examined and palpated. The upper and lower eyelid conjunctiva should be inspected for a papillary reaction or presence of a foreign body. Lastly, fluorescein should be placed in both eyes and examined under an appropriate blue light for any staining that would indicate corneal involvement (**Fig. 4**).

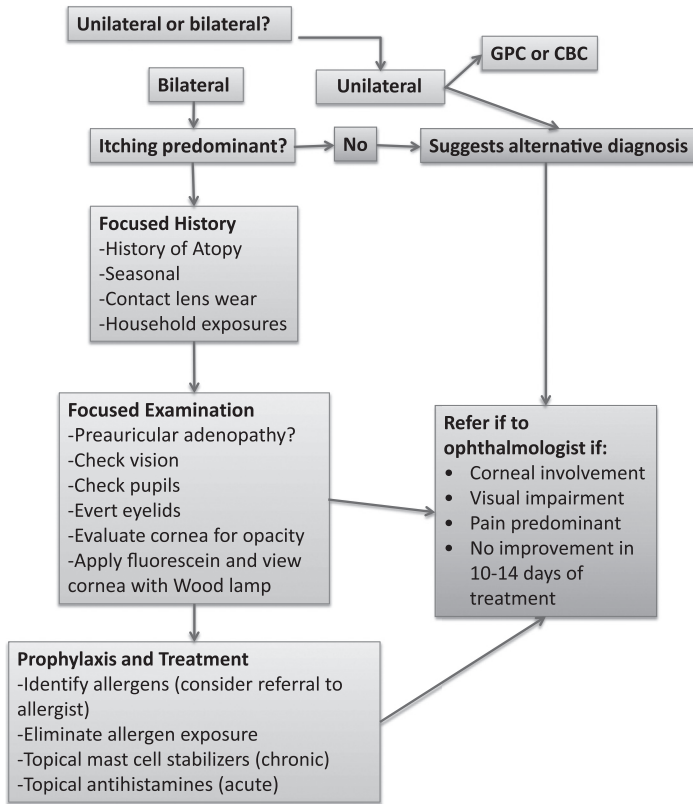


Fig. 4. Clinical evaluation and diagnostic algorithm for pediatric patients presenting with possible allergic conjunctivitis. CBC, contact blepharoconjunctivitis; GPC, giant papillary conjunctivitis.

Differential Diagnosis

The differential diagnosis includes infectious conjunctivitis, autoimmune origin (uveitis, scleritis), dry eye syndrome, and, rarely, congenital glaucoma. Distinguishing historical and examination findings are listed in [Table 3](#).

MANAGEMENT

Avoidance of the offending antigen is the primary behavioral modification for all forms of allergic conjunctivitis. An allergist may be helpful in determining the specific allergens involved in severe cases by skin testing or radioallergosorbent test (RAST). Artificial tears can help to dilute the allergens and inflammatory agents and cool compresses may help in initial supportive management. When avoidance strategies and nonpharmacologic measures fail to control symptoms, over-the-counter (OTC) and prescription topical pharmacologic agents may be considered ([Table 4](#)). The mainstays of topical treatment by nonophthalmologists are largely antihistamines and mast cell stabilizers. In general, second-generation antihistamines are superior to that of first-generation antihistamines (see [Table 4](#)). Lodoxamide is more potent than cromoglycate in stabilizing mast cells and is faster acting [102]. Combination drugs

Table 3 Differential diagnosis of allergic conjunctivitis			
	Examples	Historical	Examination
Infectious conjunctivitis	Viral conjunctivitis	Sick contacts	Preauricular
	Bacterial conjunctivitis	Upper respiratory infection may accompany	Lymphadenopathy
	Fungal or parasitic conjunctivitis	Eyes are involved sequentially rather than simultaneously	Copious mucinous or green discharge
Autoimmune mechanism	Uveitis	No itching	May have decreased vision
	Scleritis	May have systemic symptoms (joint/tendon pain) Ask about floaters Severe eye pain (scleritis) especially with ocular movements	Systemic signs May be unilateral or bilateral
Dry eye syndrome	Aqueous tear deficiency	No itching (unless ocular allergy superimposed)	Overlapping features with ocular allergy
	Tear film instability	Ask about medications that decrease tear production	
Congenital glaucoma		Age <2 y	Enlarged cornea
		Family history (usually autosomal recessive, so usually no history)	Cloudy cornea (glossy appearance)
		Tearing	Corneal asymmetry
		Photophobia	

such as olopatadine, ketotifen, and epinastine are efficacious in controlling both acute symptoms (H1 action) and prophylaxis (mast cell stabilization), and also increase adherence because of reduced dosing frequency. Topical decongestants should be avoided (oxymetazoline, naphazoline, tetrahydrozoline, phenylephrine). Although they cause vasoconstriction and can reduce erythema initially, rebound hyperemia and contact blepharoconjunctivitis can occur with acute and prolonged use respectively.²⁶ In general, topical NSAIDs and immunosuppressive agents (steroids, tacrolimus) should be prescribed by an ophthalmologist.

In terms of systemic treatment, first-generation antihistamines are not recommended because of their sedative affects and anticholinergic activity. However, second-generation antihistamines are widely used for allergic rhinoconjunctivitis and can be prescribed if systemic symptoms warrant. Importantly, systemic second-generation antihistamines can cause aqueous tear deficiency and dry eye symptoms that may actually exacerbate the ocular symptoms.²⁷

SEQUELAE OF THE PROBLEM

Resolution depends on avoidance of allergen and/or compliance with appropriate treatment. The most serious sequelae are corneal involvement that can lead to scarring and visual acuity impairment. With the breakdown of epithelium with corneal involvement, the patient has increased susceptibility to bacterial or viral infections of the cornea. Evidence of corneal involvement or impaired vision should prompt referral to an ophthalmologist.

Table 4
Topical medications for allergic conjunctivitis

	Example Medications		Indications	
Drug Class	Within Drug Class	Mechanism	Limitations/Complications	Selected Agents Dosing Requirements
Topical antihistamines	First generation: Antazoline Pheniramine Second generation: Levocabastine Emedastine	Competitively and reversibly bind histamine receptors No effect on proinflammatory mediators (PGs, LTs)	Acute treatment	Levocabastine, 1 drop q6h (≥ 12 y) Emedastine, 1 drop q6h (≥ 3 y)
			Compliance (high dosing frequency with limited duration of action)	
Mast cell stabilizers	Cromoglycate Lodoxamide	Decrease in degranulation of mast cells, which prevents release of histamine and other chemotactic factors	Prophylaxis (requires a loading period 2–3 wk before antigen exposure)	Cromoglycate, 1 drop q6h (≥ 2 y) Lodoxamide, 1 drop q6h (≥ 2 y) Start 2–3 wk before allergen exposure ^a
			Compliance (high dosing frequency and need for loading period before symptoms improve)	
Multimodal allergic agents	Olopatadine ^b	Selective H1 antagonist Mast cell stabilizer	Acute treatment Prophylaxis	Olopatadine, 1 drop q12h (≥ 3 y) ^b Ketotifen, 1 drop q8h (≥ 3 y) Azelastine, 1 drop q12h (≥ 3 y) (less relief of itching) Nedocromil, 1 drop q12h (≥ 3 y) (uncomfortable to instill, less effective than ketotifen and olopatadine) Epinastine, 1 drop q12h (≥ 3 y)
	Ketotifen	Selective H1 antagonist Mast cell stabilizer Inhibits eosinophil activation, generation of LT and cytokine release	Lower frequency of dosing	
		Azelastine		
	Nedocromil	Selective H1 antagonist Mast cell stabilizer Inhibits eosinophils		
	Epinastine	H1 and H2 antagonist Mast cell stabilizer Inhibits cytokine activation		

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Table 4
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Drug Class	Example Medications Within Drug Class	Mechanism	Indications	Selected Agents Dosing Requirements
			Limitations/Complications	
NSAIDs ^a	Ketorolac Diclofenac Flurbiprofen	Reduce expression of PG D2 and PG E2	Additive drug to reduce hyperemia and pruritus Compliance: frequent dosing Complications: Asthmatic crisis ¹¹ Corneal compromise ¹²	Ketorolac, 1 drop q6h (≥ 12 y)
Topical steroids ^a	Fluorometholone Dexamethasone Prednisolone Clobetasone Rimexolone Loteprednol	Immunosuppressive and antiproliferative properties	Short course of treatment Long-term use for severe disease	Rimexolone, 1 drop q6h (≥ 12 y) Loteprednol, 1 drop q6h (≥ 3 y)

Topical medications are not approved for children ≤ 2 years of age.

Highlighted medications are author's favorite based on literature review.^{13–25}

Abbreviations: H1, histamine type 1 receptor; H2, histamine type 2 receptor; ICAM-1, intracellular adhesion molecular 1; LT, leukotrienes; NSAIDs, nonsteroidal anti-inflammatory medications; PAF, platelet activating factor; PG, prostaglandin.

^a Agents should be prescribed by an ophthalmologist for more serious disease.

^b Formulation with once-daily dosing available.

ACKNOWLEDGMENTS

Special thanks to Adam H. Kaufman, MD, for reviewing this article and providing clinical images. Special thanks to Daniele Saltarelli, OD, for providing clinical images.

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