

Ocular Allergy Overview

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Physicians in all specialties frequently encounter various forms of allergic diseases of the eye that present as “red eyes” in their general practice. However, the allergist or clinical immunologist is trained uniquely to understand and manage atopic disorders, because the eye is rarely the only target for an immediate allergic-type response. Typically, many patients have other atopic manifestations, such as rhinoconjunctivitis, rhinosinusitis, asthma, urticaria, or eczema. However, ocular signs and symptoms may be the initial and most prominent features of the entire allergic response that patients present to their physician.

The prevalence of allergies has been increasing during the past several decades, and ranges have been reported as up to 30%–50% of the United States population [1–4]. Industrialized countries report higher allergy prevalence, correlating to the original reports of “vernal catarrh” in Great Britain after the industrial revolution. Many theories abound regarding the increasing prevalence of allergies in the United States, such as the increased industrialization, pollution, urbanization, and the “hygiene theory.” The combination of allergic nasal and ocular symptoms (rhinoconjunctivitis) is extremely common (double that of allergic rhinitis symptoms alone), but it is not clear if they are equal (ie, if rhinitis is more common than conjunctivitis or if conjunctivitis is more common than rhinitis). In studies of allergic rhinitis, allergic conjunctivitis is reported in over 75% of patients, while asthma was reported in the range of 10%–20% [5]. However, in some studies that report a high prevalence of seasonal allergic rhinitis in the United States, the ratio of ocular to nasal symptoms appears to double throughout all sections of the United States [6]. Thus, the eye is probably the most common site for the development of allergic inflammatory disorders, because allergens can directly impact on the eye’s surface. Ocular allergy commonly is found in conjunction with allergic rhinitis, which is considered the

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most common allergic disorder. Although the nasal and ocular symptoms (more appropriately called “conjunctivorhinitis”) are perceived as a mere nuisance, their consequences can profoundly affect the patient’s quality of life. Seasonal allergic rhinitis and conjunctivitis has been associated with headache and fatigue, impaired concentration and learning, loss of sleep, and reduced productivity [7,8]. Patients also may suffer from somnolence, functional impairment, and increased occupational risks for accidents or injuries secondary to sedating oral antihistamine therapy. In 70% of seasonal allergy patients, conjunctivitis symptoms are at least as severe as rhinitis symptoms [9].

The ocular surface

Allergens and other ocular irritants are deposited easily directly on the surface of the eye. Many agents that are systemically absorbed also can be concentrated and secreted in tears, causing allergic conjunctivitis or an irritant form of conjunctivitis [10]. The overuse of vasoconstrictive agents may lead to a form of conjunctivitis medicamentosa in some patients [11,12]. Other causes of the red eye also may include intraocular conditions associated with systemic autoimmune disorders such as uveitis or scleritis [13]. In addition, allergic inflammatory disorders, such as those that may affect surrounding skin, mucosa or even sinuses and release various mediators of inflammation, including histamine, leukotrienes, and neuropeptides, can have effects on the local ocular tissue [14].

Clinical examination

The clinical examination of the eyes for signs of ocular allergy requires an evaluation of the periorbital tissue and the eye itself. The eyelids and eyelashes are examined for the presence of erythema on the lid margin, telangiectasias, scaling, thickening, swelling, collarettes of debris at the base of the eyelashes, periorbital discoloration, blepharospasm, or ptosis, which are seen in blepharoconjunctivitis and dermatoconjunctivitis. Next, the conjunctivae are examined for hyperemia (injection), cicatrization (scarring), and chemosis (clear swelling). The presence or absence of discharge from the eye is noted for amount, duration, location, and color. The differentiation between scleral injection (scleritis) and conjunctival injection is that scleritis tends to develop over several days and is associated with moderate or severe ocular pain on motion, whereas conjunctivitis is associated with discomfort, but not pain. Scleritis commonly develops in patients who have autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and Wegener’s granulomatosis, but it has been known to occur alone without any other obvious clinical disorders [15–17]. Another form of ocular injection is described as a ring of erythema around the limbal junction of the cornea (ciliary flush), which is a clinical sign for intraocular

inflammation such as uveitis. The conjunctival surface also should be examined closely for the presence of inflammatory follicles or papillae involving the bulbar and tarsal conjunctivae. Follicles can be distinguished as grayish, clear, or yellow bumps varying in size from pinpoint to 2 mm in diameter with conjunctival vessels on their surface, whereas papillae contain a centrally located tuft of blood vessels [18]. The cornea is involved rarely in acute forms of allergic conjunctivitis, whereas in the chronic forms of ocular allergy such as vernal keratoconjunctivitis and atopic Keratoconjunctivitis, the “kerato” reflects that the cornea is involved.

Optimal examination of the cornea is completed with the slit-lamp biomicroscope, although many important clinical features can be seen with the naked eye or with the use of a hand-held direct ophthalmoscope. The direct ophthalmoscope can provide the desired magnification by “plus” (convex) and “minus” (concave) lenses. The cobalt blue filter on the new hand-held ophthalmoscopic heads assists in highlighting anatomic anomalies affecting the cornea or the conjunctiva that have been stained with fluorescein. The cornea should be perfectly smooth and transparent. Mucus adhering to the corneal or conjunctival surfaces is considered pathologic. Dusting of the cornea may indicate punctate epithelial keratitis (a condition commonly seen in chronic eosinophilic conditions of conjunctiva). A localized corneal defect may develop into erosion or a larger ulcer. A corneal plaque may be present if the surface appears dry and white or yellow. The limbus is the zone immediately surrounding the cornea and is normally invisible to the naked eye, but when inflamed, this area becomes visible as a pale or pink swelling. There have been some case reports of limbal allergy [19]. Discrete swellings with small white dots (Trantas-Horner’s dots) are indicative of degenerating cellular debris that is seen commonly in chronic forms of conjunctivitis. In addition, since the eye has thin layers of tissue surrounding it, there is an increased tendency to develop secondary infections that can complicate further the clinical presentation [20,21].

Immunopathophysiology of ocular allergy

Allergic diseases affecting the eyes constitute a heterogeneous group of clinicopathologic conditions with a vast array of clinical manifestations that range from simple intermittent symptoms of itching, tearing, or redness, to severe sight-threatening corneal impairment. These conditions may be considered as part of an immunologic spectrum that affects the anterior surface of the eye with a variety of disorders that may overlap and may include seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC) [22]. In addition, tear film dysfunction (otherwise known as dry eye syndrome [DES]), commonly complicates ocular allergy and its treatments, especially as the

age of the patient increases and is included to reflect the spectrum of hypersensitivity responses from immunoglobulin E (IgE) mast cell hypersensitivity conditions to a mixture of mast cell and cell mediated disorders that involve different mechanisms, cytokines, and cellular populations [23–25]. For example, mast cell degranulation [26–28] and histamine release [29–33] play key roles with limited eosinophil involvement [34–36] in the common forms of SAC and PAC, whereas AKC and VKC are characterized by more chronic inflammatory cellular infiltrates primarily composed of Th2 lymphocytes with an interplay with activated mast cells and eosinophils, and tear film dysfunction, a Th1 mediated disorder, commonly can overlap ocular allergy syndromes (Table 1) [37–39].

Mast cell mediators such as histamine, tryptase, leukotrienes, and prostaglandins in the tear fluid have diverse and overlapping biologic effects [40–42], all of which contribute to the characteristic itching, redness, watering, and mucous discharge associated with both acute and chronic allergic eye disease. Histamine alone has been shown to be involved in the regulation of vascular permeability, smooth muscle contraction, mucus secretion, inflammatory cell migration, cellular activation, and modulation of T-cell function. Histamine is a principal mediator involved in ocular allergy and inflammation [29,32]. In fact, it is estimated that human conjunctival tissue contains approximately 10,000 mast cells per mm³ [23,39]. Large amounts of histamine are present in several mammalian ocular structures, including the retina, choroid, and optic nerve. Histamine receptors have been found on the conjunctiva, cornea, and ophthalmic arteries. Two separate histamine receptors, H1 and H2, have been identified in the conjunctiva [43–46]. Most ocular allergic reactions are mediated through the effects of histamine on H1 receptors. Histamine concentration in tears of allergic conjunctivitis patients can reach values greater than 100 ng/mL as compared with values of 5–15 ng/mL in controlled patients. Histamine can induce changes in the eye similar to those seen in other parts of the body. These changes include capillary dilatation leading to conjunctival redness, increased vascular permeability leading to chemosis, and smooth-muscle contraction.

In the more severe chronic allergy-related conditions, T cells are the key cellular players in ocular surface impairment, with two predominant inflammatory pathways differentiated by the TH1 and TH2 cell markers, which involve different cytokines and are crudely considered as antagonistic of each other when activated. In previous reports based on conjunctival biopsies in allergic patients, cytokine profiling displayed that TH2 activation occurred in VKC, whereas both TH1 and TH2 activation were found in AKC [39,47–50]. In addition, it is not rare that a patient who is treated for typical SAC also may develop dry eye, tear film disturbance, meibomian dysfunction, adverse effects from the repeated use of toxic preservative-containing topical drugs, or contact cell-mediated conjunctival or eyelid hypersensitivity, all of which are conditions linked to the TH1 cascade [37,51–53].

Table 1
Differential diagnosis of conjunctival inflammatory disorders

	AC	VKC	AKC	GPC	DCS	Bacterial	Viral	CHLMD	DES	BC
Signs										
Predominant cell types	Mast cell eosinophils	Lymphocyte eosinophils	Lymphocyte eosinophils	Lymphocyte eosinophils	Lymphocyte eosinophils	PMN	PMN mono cyte lymphocytes	Monocyte lymphocytes	Lymphocyte monocytes	Monocyte lymphocytes
Chemosis	+	±	±	±	–	±	±	±	–	±
Lymph node	–	–	–	–	–	+	++	±	–	–
Cobblestoning	–	++	++	++	–	–	±	+	–	–
Discharge	Clear mucoid	Stringy mucoid	Stringy mucoid	Clear white mucoid	±	++ Muco-purulent	Clear mucoid	++ Muco-purulent	± Mucoid	++ Muco-purulent
Lid involvement	–	+	+	–	++	+ Glue lids	–	–	–	++
Symptoms										
Pruritus	+	++	++	++	+	–	–	–	–	+
Burning	–	–	–	–	–	–	++	+	+	–
Gritty sensation	±	±	±	+	–	+	+	+	+++	++
Seasonal variation	+	+	±	±	–	±	±	±	–	–

The differential diagnosis of the red eye includes various inflammatory conditions that involves the outside and the inside of the eye. [Table 1](#) focuses on the signs and symptoms of external causes of the red eye that include the predominant cell type found in the conjunctival scraping and the presence or absence of chemosis, lymph node involvement, cobblestoning of the conjunctival surface, discharge, lid involvement, pruritus, gritty sensation, and seasonal variation. *Abbreviations:* AC, allergic conjunctivitis; AKC, atopic keratoconjunctivitis; BC, blepharoconjunctivitis; CHLMD, chlamydial infection; DCS, dermatocconjunctivitis; DES, dry eye syndrome; GPC, giant papillary conjunctivitis; PMN, polymorphonuclear cell.

From Bielory L. Allergic diseases of the eye. Med Clin North Am 2006;90(1):129–48; with permission.

Acute allergic conjunctivitis

The eye actually may be the most common target organ of IgE mast cell hypersensitivity mediated reactions [54]. Allergic conjunctivitis is caused by the direct exposure of the ocular mucosal surfaces to environmental allergens (such as pollens from trees, grasses, and weeds) interacting with the pollen-specific IgE found on the mast cells of the eye. Of all the various pollens, ragweed has been identified as the most common cause of conjunctivitis in the United States, approaching 75% of all cases of “hay fever” with variations of prevalence in different age groups in various regions of the world [6,55–57]. In the earliest studies on allergy testing, Timothy grass has been identified as one of the most potent ocular allergy inducing allergens [58]. Common conjunctival symptoms include itching, tearing, and perhaps burning. Involvement of the cornea is rare, with blurring of vision being the most common corneal symptom [18,59]. Clinical signs include a milky or pale pink conjunctiva with vascular congestion that may progress to conjunctival swelling (chemosis). A white exudate may form during the acute state and becomes stringy in the chronic form. While ocular signs are typically mild, the conjunctiva frequently takes on a pale, boggy appearance that often evolves into diffuse areas of papillae (small vascularized nodules). These papillae tend to be most prominent on the superior palpebral conjunctiva. Occasionally, dark circles beneath the eyes (allergic shiners) are present as a result of localized venous congestion [60]. PAC, like perennial allergic rhinitis, also exhibits the classic IgE mast cell-mediated hypersensitivity to airborne allergens, which is more commonly sensitive to common perennial household allergens, such as dust mites, molds, and animal dander instead of grass or weed pollens, as with patients who have SAC [61–65]. The ocular reaction seen in both SAC and PAC often resolves quickly once the offending allergen is removed. Obtaining a detailed history from the patient can make the diagnosis of these disorders. Both eyes typically are affected simultaneously, and quite often, a family history of hay fever or atopy is elicited.

Vernal keratoconjunctivitis

VKC is a chronic mast cell/lymphocyte-mediated allergic disorder of the conjunctiva that appears more in males before pubescence, after which it is equally distributed among the sexes and then commonly “burns out” approximately 10 years later (ie, in the third decade of life). As the name implies VKC is recurrent seasonally in the spring (vernal) with symptoms that include intense pruritus induced by nonspecific stimuli, such as exposure to wind, dust, bright light, hot weather, or physical exertion associated with sweating [38]. Although considered a form of ocular allergy, over 50% of patients have a negative skin test or a radioallergosorbent test to allergens [66]. As in other chronic ocular allergy conditions, conjunctival biopsies

reveal increased numbers of eosinophils, basophils, and mast cells, and increased numbers of plasma cells and lymphocytes that result with increased corneal involvement with photophobia, foreign body sensation, and lacrimation [39,67]. The most remarkable physical finding is “giant” papillae on the tarsal conjunctiva reaching 7–8 mm in diameter of the upper tarsal plate, which can result in the “cobblestone” appearance on examination [68]. In addition, patients may develop a thin copious milk-white fibrinous secretion, limbal or conjunctival “yellowish-white points” (Horner’s points and Trantas’ dots), an extra lower eyelid crease (Dennie’s line), corneal ulcers, or pseudomembrane formation of the upper lid when everted and exposed to heat (Maxwell-Lyons’ sign) [60]. The effects of VKC can be so severe that blindness may result, affecting one eye more than the other in approximately 5% of patients [67,69]. Diffuse areas of punctate corneal epithelial defects can occur in some cases. These defects are best appreciated with a cobalt blue light after the instillation of topical fluorescein dye [70]. In severe cases, these superficial punctate defects may progress to “shield ulcers”, which are areas of desquamation of epithelial cells caused by the release of major basic protein from infiltrating eosinophils [71,72].

Atopic keratoconjunctivitis

AK is a chronic inflammatory process and a chronic mast cell/lymphocyte-mediated allergic disorder of the conjunctiva of the eye periorbital tissue that is associated with a familial history for atopy, such as eczema and asthma [73,74]. Allergists or clinical immunologists should expect to see approximately 25% of their elderly patients who have eczema develop some components of AKC. Although AKC commonly is seen in individuals older than 50 years of age, onset can be in selected individuals as early as the late teens. AKC is an eye disorder with disabling symptoms; when it involves the cornea, it can lead to blindness [67]. Ocular symptoms of AKC are similar to the cutaneous symptoms of eczema and include intense pruritus and edematous, coarse, and thickened eyelids. Severe AKC is associated with complications such as blepharoconjunctivitis, cataract, corneal disease, and ocular herpes simplex [75,76]. The symptoms of AKC commonly include itching, burning, and tearing, which are much more severe than in acute conjunctivitis or PAC and tend to be present throughout the year. Seasonal exacerbations are reported by many patients, especially in the winter or summer months, and include exposure to animal dander, dust, and certain foods [38,70,77]. Ocular disease activity has been shown to correlate with exacerbations and remissions of the dermatitis. AKC associated cataracts occur in approximately 10% of patients who have the severe forms of atopic dermatitis, but they occur especially in young adults approximately 10 years after the onset of the atopic dermatitis. A unique feature of AKC cataracts is that they predominantly involve the anterior portion of the lens and may evolve rapidly into complete opacification within 6 months, whereas AKC patients

may develop posterior polar type cataracts caused by the prolonged use of topical or oral corticosteroid therapy [78–82]. Keratoconus occurs in a small percentage of patients who have atopic dermatitis. Retinal detachment appears to be increased in patients who have AKC, although it also is increased in patients who have atopic dermatitis in general. The association with specific microorganisms, such as *S aureus* is under investigation presently [20,83,84]. Treatment involves corticosteroids, antihistamines, mast cell stabilizers, and treatment of systemic features of atopic dermatitis. There is a heightened concern regarding the use of antihistamines in older patients who have this condition, because antihistamines may increase dryness of the conjunctival surface.

Giant papillary conjunctivitis

GPC is not truly an “ocular allergy,” but many of its features mimic those of the other ocular hypersensitivity syndromes (ie, an increase of symptoms during the spring pollen season and pruritus); thus, it is important to include GPC in the differential diagnosis of ocular allergy [54,85,86]. GPC is becoming more common with the advent of extended-wear soft contact lenses and other foreign bodies, such as suture materials and ocular prosthetics. Symptoms include a white or clear exudate upon awakening, which chronically becomes thick and stringy, and the patient may develop papillary hypertrophy (“cobblestoning”) especially in the tarsal conjunctiva of the upper lid, which is more common in soft (~5%–10%) versus hard contact (~4%) lens wearers. The contact lens polymer and preservatives such as thimerosal and proteinaceous deposits on the surface of the lens have been implicated as causing GPC, but this concept remains controversial [87–90]. Common symptoms include intense itching, decreased tolerance to contact lens wear, blurred vision, conjunctival injection, and increased mucous production. Treatment involves use of corticosteroids, antihistamines, and mast cell stabilizers and frequent enzymatic cleaning of the lenses, or changing of the lens polymers. Disposable contact lenses have been proposed as an alternative treatment for GPC. It will usually resolve when the patient stops wearing contact lenses or when the foreign body is removed.

Dry eye syndrome (tear film dysfunction)

DES, also known as tear film dysfunction, develops from decreased tear production, increased tear evaporation, or an abnormality in specific components of the aqueous, lipid, or mucin layers that comprise the tear film [91–94]. Symptoms of DES are typically vague and include foreign body sensation, easily fatigued eyes, dryness, burning, ocular pain, photophobia, and blurry vision. Patients initially complain of a mildly injected eye with excessive mucous production and symptoms of gritty sensation as compared with the itching and burning feeling many patients complain of with

histamine release onto conjunctiva. Symptoms tend to be worse late in the day after prolonged use of the eyes or exposure to environmental conditions.

Whereas DES may occur as a distinct disorder resulting from intrinsic tear pathology, it is associated more frequently with other ocular and systemic disorders, including ocular allergy, chronic blepharitis, fifth or seventh nerve palsies, vitamin A deficiency, pemphigoid, and trauma [95]. DES is a frequent confounding disorder that may complicate ocular allergic disease with several overlapping signs and symptoms, such as tearing, injection, and exacerbations [96,97]. As the cornea becomes involved, a more scratchy and painful sensation and photophobia may appear. DES and ocular allergy conditions are not exclusive, and as patients age, the likelihood that tear film dysfunction complicating ocular allergies increases [98]. A more systemic form of DES associated with systemic immune diseases (such as Sjögren's syndrome, rheumatoid arthritis or HIV infection [99]) is known commonly as keratoconjunctivitis sicca or hormonal dysregulation that is commonly found in postmenopausal women [100]. The most common cause of DES is not associated with an autoimmune disorder, but rather, the use of medications with anticholinergic properties that decrease lacrimation. Many drugs with antimuscarinic properties include the first-generation antihistamines and even newer agents, such as loratadine and cetirizine [101], phenothiazines, tricyclic antidepressants, atropine, and scopolamine. Other agents that are associated with a sicca syndrome include the retinoids, beta blockers, and chemotherapeutic agents. Tear film dysfunction also is associated with several pharmacologic agents, including antihistamines, anticholinergics, and some psychotropic agents [102]. Exacerbation of symptoms also occurs in the winter months when heating systems decrease the relative humidity in the household to less than 25%. Diagnostic evaluation includes use of the Schirmer test, which typically demonstrates decreased tearing (0–1 mm of wetting at 1 minute and 2–3 mm at 5 minutes). Normal values for the Schirmer test are more than 4 mm at 1 min and 10 mm at 5 min. Treatment includes addressing the underlying pathology, discontinuing the offending drug if possible, and generous use of artificial tears or ocular lubricants. The use of topical cyclosporine has been approved by the FDA for the treatment of DES [37,103]. For severe symptoms, insertion of punctal plugs may be indicated [104].

Contact dermatitis of the eyelids

In contradistinction to ocular allergy, with its predominant activation of the IgE mast cell, contact dermatitis is predominantly a delayed type of lymphocytic hypersensitivity reaction involving the eyelids and the conjunctiva [54,105–107]. The eyelid skin is extremely thin, soft, and pliable and is capable of developing significant swelling and redness with minor degrees of inflammation. This frequently causes the patient to seek medical attention for a cutaneous reaction that, had it appeared elsewhere on the

skin, normally would be less of concern. Two principal forms of contact dermatitis attributable to eye area cosmetics are recognized: contact dermatitis and irritant (toxic) contact dermatitis. Contact dermatitis commonly is associated with either cosmetics applied to the hair, face, or fingernails (eg, hair dye and nail polish) or topical ocular medications (eg, neomycin) [108,109]. Preservatives such as thimerosal, found in contact lens cleaning solutions, and benzalkonium chloride, found in many topical ocular therapeutic agents, have been shown by patch tests to be major culprits like the active drugs themselves [110–118]. Stinging and burning of the eyes and itching of the lids are the most common complaints. These subjective symptoms are usually transitory and unaccompanied by objective signs of irritation. The patch test can assist in pinpointing the causative antigen, but interpretation of patch-test results consequently may be difficult, and the likelihood of irritant false-positive reactions must be kept in mind [119–121].

Blepharoconjunctivitis

Blepharitis is a primary inflammation of the eyelid margins that is most often misdiagnosed as an ocular allergy, because it commonly causes conjunctivitis in a secondary fashion [54,110,122–124]. The primary etiologies are various infections or seborrhea. In general, as is also found in patients who have atopic dermatitis, the most common organism isolated from the lid margin is *Staphylococcus aureus*. It has been suggested that antigenic products play the primary role in the induction of chronic eczema of the eyelid margins [20,125–128]. The symptoms include persistent burning, itching, tearing and “a feeling of dryness.” Patients commonly complain of more symptoms in the morning than in the evening. This is in contradistinction to patients who have DES and who complain of more symptoms in the evening than in the morning, because the tear film dries out during the day. The crusted exudate that develops in these patients may cause the eye to be “glued shut” when the patient awakens in the morning. The signs of staphylococcal blepharitis include dilated blood vessels, erythema, scales, collarettes of exudative material around the eyelash bases, and foamy exudates in the tear film. Blepharitis can be controlled with improved eyelid hygiene with detergents (eg, nonstinging baby shampoos) and with steroid ointments applied to the lid margin with a cotton tip applicator that loosens the exudate and scales.

Bacterial conjunctivitis

Ocular irritation, conjunctival redness, and a mucopurulent discharge that is worse in the morning characterize acute bacterial conjunctivitis. The absence of itching should indicate an infectious cause of conjunctivitis,

such as bacterial or viral [129]. In bacterial conjunctivitis, the eyelids usually become matted to each other; this is noted primarily in the morning when the patient awakens. There is a large accumulation of polymorphonuclear cells on the surface of the eye that causes the discharge to become discolored (yellowish green). Scraping and culturing of the palpebral conjunctiva can assist with the diagnosis and treatment with the appropriate topical antibiotic regimens.

Some forms of bacterial infection, such as inclusion conjunctivitis, that have been associated with chlamydial infections are associated with a preauricular node. Common findings of inclusion conjunctivitis include a mucopurulent discharge and follicular conjunctivitis lasting for more than 2 weeks [130]. A Giemsa stain of a conjunctival scraping may reveal intracytoplasmic inclusion bodies and will assist in confirming the diagnosis. In addition, such prolonged ocular infections commonly are associated with a conjunctival response that reveals grayish follicles on the upper palpebra. The condition can be chronic, and treatment consists of lid margin scrubs, warm compresses, and antibiotics. In general, a topical, broad-spectrum antibiotic (such as sulfacetamide, erythromycin, or a combination of polymyxin B, bacitracin and Neosporin) is appropriate. Cultures are necessary only if the conjunctivitis is severe; it would be best if cultures were examined carefully by an ophthalmologist. The condition should be followed carefully to ensure that the eye improves [131].

Topical gentamicin and tobramycin are indicated if Gram-negative organisms are suspected or seen on Gram stain. All of these antibiotics have the potential to elicit an allergic reaction. A careful history of drug allergies and a time limit for therapy and re-evaluation will minimize complications. Topical ciprofloxacin or ofloxacin offer coverage for a wide spectrum of infecting agents, but they should be used only when there is a likelihood for therapeutic failure or if the conjunctivitis is thought to be caused by multiple infecting organisms or *Pseudomonas* sp [132]. Treatment of inclusion conjunctivitis should be aggressive, because there is the potential for the cornea to perforate in a short time. Both topical and systemic antibiotics should be used. The patient should be observed for other sexually transmitted diseases.

Viral conjunctivitis

Viral conjunctivitis usually has an acute onset, is unilateral, and lasts for approximately one week, but it frequently becomes bilateral [129]. A major clinical symptom that differentiates viral conjunctivitis from allergic conjunctivitis is burning and absence of itching. Adenoviral infections are among the most common viral ocular infections and are extremely contagious. The viral infection produces an inferior follicular response and a serous discharge. It also may involve the cornea as a punctate keratopathy or superficial ulcerations (herpes simplex or herpes zoster infections) [133].

Common findings of viral conjunctivitis include a watery discharge, conjunctival injection, chemosis, and enlargement of the preauricular (pretragal) lymph nodes [129]. Patient history also assists in the diagnosis. Viral conjunctivitis usually is transmitted between family members or among school children. As in chronic bacterial infections, gray elevated vascular areas, known as lymphoid follicles, also may be present. A more serious form of viral conjunctivitis is that caused by herpes simplex, which is one of the leading infectious causes of blindness in Western countries. The viral infection produces an inferior follicular response and a serous discharge, and it can occur without any other sign of a herpetic infection. The pain associated with herpetic infections is excruciating. The pain can occur days before the lesions appear. The absence of pruritus should guide the clinician away from a diagnosis of allergic eye disease and toward an infectious complication. Viral conjunctivitis also may involve the cornea in the form of punctate keratopathy or the classic “dendritic” superficial ulcerations. The possibility of herpes keratitis is one of the most compelling reasons for a primary care physician to examine the cornea with fluorescein staining. Treatment of nonspecific viral conjunctivitis is largely supportive and requires no drug therapy. Topical vasoconstrictors may provide symptomatic relief, and they may decrease conjunctival injection. If the corneal epithelium becomes compromised and there is a risk for secondary infection, prophylactic antibiotics may be indicated [134,135].

Vasomotor conjunctivitis

Mismatches between history and IgE sensitization have been recognized since the use of conjunctival and cutaneous tests in the 1930s. Interestingly, asymptomatic skin cutaneous reactivity appears to be associated with evolution to allergic diathesis, especially when it is paralleled with late phase response that is also associated with the development of a positive conjunctival provocation and increased IL-5 expression and eosinophil proliferation [136,137].

The first use of the term “vasomotor conjunctivitis” can be found in Russian literature from 1971 [138,139]. The possibility of a link between vasomotor rhinitis and conjunctivitis interestingly was reported with bulbar vessel enlargement, diameter nonuniformity, pathologic convolution, and red blood cell aggregation. However, this was noted in a pediatric population, aged 6 to 15 years, that is not known to have a high prevalence of vasomotor [140]. The existence of a nonspecific hyper-reactivity of the conjunctiva to a number of physical agents (ie, temperature [hot and cold air], light, water, dust, and particulate matter [smoke and odors]) chemical agents (eg, volatile organic chemicals) and pharmacologic agents in a common characteristics of allergic subjects, which is strictly related to the inflammatory events consequent to an allergic reaction [139]. The existence of nonallergic hyper-reactivity of the conjunctival surface resurfaced in

the literature [49] and subsequently evaluated using a 40% glucose hyperosmolar solution in a conjunctival provocation model that clearly demarcated between normal, allergic conjunctivitis, and nonspecific conjunctival hyperactivity [141]. Such nonallergic stimuli also have been reported to be associated with mast cell mediator release and have been seen in other allergic target organs such as the nose and lung.

Nonallergic ocular hypersensitivity may overlap ocular allergy, as suggested in various studies noted above and in studies of airline crewmembers during the time when smoking had been permitted; the prior history of atopy in the airline crew members was a factor in the development of ocular symptoms (11%) and other symptoms such as fatigue (21%), nasal symptoms (15%), dry or flushed facial skin (12%), and dermal hand symptoms (12%). The aircrew that had a history of atopy had an increase of most symptoms (OR = 1.5–3.8) [142]. In addition, in studies of various large corporate buildings without previously recognized indoor air problems, frequent symptoms included a feeling of eye irritation, fatigue, or heavy-headedness and dry facial skin. Women reported symptoms more frequently than men. Employees who had allergies had a 1.8–2.5 higher risk of reporting a high score for general, skin, or mucosal symptoms.

As with other analyses on ocular allergy, the epidemiologic evidence is cloaked in nasal allergy literature. As one examines the literature regarding nonallergic rhinitis, there is a range of reports from 25 up to 52% in a pediatric population [143–145]. However, many health care observers recognize that patients may have coexisting allergic and nonallergic disease, and in a retrospective analysis of a broader set of patients attending an allergy clinic, 43% of patients had allergic rhinitis, 23% nonallergic rhinitis, and 34% mixed rhinitis. Importantly, 44% of the patients who had been diagnosed with allergic rhinitis also had a nonallergic element. Regarding the nonallergic element, some doctors have tried to explain it as an immune response to viral or bacterial infections of the conjunctiva, an irritant response to a chemical, or a defect in the physiologic homeostasis of the conjunctival surface. An examination of the possible triggers of the nonallergic element creating mucosal hypersensitivity reactions at the conjunctival surface have been reported in several epidemiologic studies focusing on traffic pollution [146–156]. In vitro laboratory findings indicate that diesel exhaust particles can act as an adjuvant and actually enhance IgE production and sensitivity to allergens [146–156]. In other studies of ocular allergy patients who had positive clinical histories that were confirmed by skin testing and then nasal or ocular provocation, there was a constant percentage of patients (24%) who had positive histories but negative serologic or provocation [157].

Ocular examination

The ocular examination begins with the eyelids and lashes. One should look for evidence of lid margin erythema, telangiectasia, thickening, scaling,

and lash collars. Then the sclera and conjunctiva are examined for the presence of redness (injection). Certain characteristics that assist in pinpointing the diagnosis are characterized below.

Subconjunctival hemorrhages spontaneously occur after coughing, sneezing, or straining as a result of spontaneous rupture of a conjunctival or episcleral capillary. It is characterized by a painless focal area of solid redness surrounded by normal white sclera on all sides. It commonly resolves without any intervention.

A fundamental principle of the ocular examination is determining whether conjunctival inflammation is nonspecific or punctuated by the presence of follicles or papillae involving the bulbar and tarsal conjunctiva. Follicles appear as grayish, clear, or yellow bumps varying in size from pinpoint to 2mm in diameter, with conjunctival vessels on their surface that generally are distinguishable from papillae that contain a centrally located tuft of vessels that can be seen in the center of papilla as a "red spot." Although a fine papillary reaction is nonspecific, giant papillae (greater than 1mm) on the upper tarsal conjunctiva indicate an allergy and are not seen in active viral or bacterial conjunctivitis. Follicles, a lymphocytic response in the conjunctiva, are a specific finding that occurs primarily in viral and chlamydial infections. Follicle formation is normal in childhood, but in adults, it may indicate significant conjunctival inflammation in the form of viral conjunctivitis (such as adenoviral or primary herpetic conjunctivitis) or chlamydial infection. For a clinician to determine an acceptable (nonpathologic) level of follicular and papillary reactivity, it is advised that they examine the upper and lower tarsal plates and bulbar conjunctiva on a routine basis. Reactive lymphoid hyperplasia is indicated by firm to rubbery nodules under the conjunctiva and without acute inflammatory signs such as erythema, chemosis, or pain.

Conjunctival injection is more intense on the palpebral conjunctiva than the bulbar conjunctiva. The intensity of the injection decreases as one approaches the cornea. In contrast to ciliary injection, the erythema increases as one approaches the cornea. Ciliary injection engorges the ciliary vessels that run one layer deeper than the conjunctiva. It usually appears as a violaceous (purplish) red ring of injection around the cornea when viewed with a handlight. In patients who have ciliary injection, the eversion of the lower eyelids usually reveals normal appearing conjunctiva. If one touches the conjunctiva with a cotton-tipped applicator, the conjunctiva moves freely and the dilated conjunctival vessels move with it. Deeper dilated vessels, such as the ciliary blood vessels, do not move freely with the conjunctiva. In addition, the placement of dilating drops (ie, vasoconstricting agents) constrict the conjunctival blood vessels, making the eye appear less red, while the deeper episcleral vessels remain dilated and engorged.

Episcleritis is the most common and important form of inflammatory disorder that affects the tunic surrounding the ocular globe. The sclera is continuous with the cornea and the lamina cribosa of the optic nerve. The sclera is composed of collagen and elastic fibers and is subject to involvement with

systemic autoimmune disorders (eg, systemic lupus erythematosus and rheumatoid arthritis). The episclera, unlike the sclera, is highly vascularized. Episcleritis is a benign self-limiting, sometimes bilateral, inflammatory process in young adults that presents as a red, somewhat painful eye with occasional watering. The inflammatory reaction is located below the conjunctiva and only over the globe of the eye. Severe pain and photophobia are not characteristic features of episcleritis.

Scleritis is much more painful than episcleritis and results in a reddish purple color. Major signs and symptoms of scleritis include moderate to severe ocular pain, tender and inflamed conjunctiva, and thickened and injected sclera. This form of inflammation may extend into the deeper portions of the eye, such as the choroid. In various forms of advanced scleritis, scleral thinning may occur in a painless variety known as scleromalacia. Scleritis tends to develop progressively over the course of several days. The presence of scleritis should prompt a search for other systemic immune mediated disorders, particularly rheumatoid arthritis and Wegener's granulomatosis.

Uveitis is a significant ocular condition that requires immediate ophthalmologic evaluation. One of the signs of this disorder is circumcorneal injection (ciliary flush), which is often described as a ring of redness that completely encircles the edge (limbus) of the cornea. Pupil size also is helpful when forming the diagnosis of a red eye. In iritis, the affected pupil is usually smaller and sluggish. In acute-angle closure glaucoma attacks, the pupil usually is mid-dilated and sluggish or fixed.

The cornea is examined next. A corneal opacity, seen as a whitish infiltrate, is often a sign of a bacterial corneal ulcer. A corneal ulcer is an ophthalmologic emergency. Fluorescein stains help to differentiate among punctate epithelial defects (diffuse punctate staining), herpes simplex keratitis (dendrite-like shaped staining), and abrasion (large solid area of staining seen after trauma).

Ophthalmic procedures and testing

Allergists and clinical immunologists also should be familiar with some ophthalmic procedures and tests to assist in completing a detailed and thorough history and physical examination, which will assist in confirming a diagnosis of ocular allergy [18,70]. More importantly, these various tests help to differentiate between the many disorders that mimic allergic disorders of the eye.

The Schirmer tear test is the most used and easily performed test for the evaluation of DES. Tear production is assessed by the amount of wetting seen on a folded strip of sterile filter paper after it is placed into the conjunctival sac. The patient is seated and the room lights are dimmed, and the patient is asked to "look up" as the lower eyelid is pulled gently downward. Excess moisture and tears are dried along the eyelid margin and conjunctiva with a sterile cotton-tipped applicator. The rounded end of the test strip is bent at the notch approximately 90°–120° and is hooked into the conjunctival

sac at the junction of the middle and lateral one third of the lower eyelid margin. The patient's eyes remain closed throughout the examination. The test strips are removed after 5 minutes. The length of the moistened area from the notch to the flat end of the sterile strip is measured using a millimeter ruler or the scale imprinted on the test strip package. Some of the test strips have a leading edge of tear film that changes color, thus improving the reading of the results. The Schirmer I test (without anesthesia) measures both basal and reflex tearing, and the Schirmer II test (with anesthesia) measures only the basal secretion of tearing and is performed as outlined above, but with topical anesthesia instilled.

Fluorescein is a water-soluble dye used to examine the cornea and conjunctival surfaces. It stains the denuded epithelium. It is placed into the eye either with a sterile fluorescein sodium ophthalmic strip or with a dropper in liquid form. A cobalt blue filter is needed to appreciate the fluorescein-staining pattern of the conjunctiva and cornea. This filter produces a blue hue against the intense green color of the fluorescein dye. The patient is asked to blink several times to spread the fluorescein uniformly and evenly over the entire corneal and conjunctival surface. Soft contact lenses must be removed before fluorescein instillation to prevent their permanent staining. At least 1 hour must pass after completion of the examination before the soft contact lenses can be replaced in the eyes.

Conjunctival scraping also can assist in differentiating various forms of red eye. After the administration of a topical local anesthetic, the palpebral conjunctiva (under the upper lid) is scraped gently several times with a spatula for cytologic examination. The sample is spread on a slide and stained with May-Grunwald, Giemsa or another orthochromatic stain to identify eosinophils or neutrophils. The absence of inflammatory cells does not rule out the diagnosis of allergic conjunctivitis, but the presence of eosinophils strongly suggests it.

Conjunctival and eyelid cultures are obtained using a sterile cotton-tipped applicator moistened in thioglycolate broth. The lower palpebral conjunctiva is wiped lightly with the applicator stick for 5 seconds as the patient is asked to look up. Moistened swabs are preferred, because they pick up and release bacteria better than do dry swabs. Then the sample is placed into the transport medium.

Ocular provocation testing can be likened to "skin testing" of the eye. Known quantities of specific allergen are instilled onto the ocular surface, and the resulting allergic response is measured. This technique is performed commonly by allergists in a research study, especially in the assessment of new drugs against ocular allergies.

Summary

The prevalence of ocular allergy clearly is underappreciated and has been under diagnosed and undertreated. The ocular symptoms associated with the

most common ocular allergy conditions, such as SAC and PAC, are twice as likely to affect the allergy sufferer rather than nasal symptoms alone. The differential diagnosis of conjunctivitis is quite broad, with the most common forms associated with allergies, infections, and hormones. There are common features and some discerning features that, with a good history and examination, may provide a more focused and appropriate management.

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