Issue 2

Clinical Perspectives

Ocular Allergies

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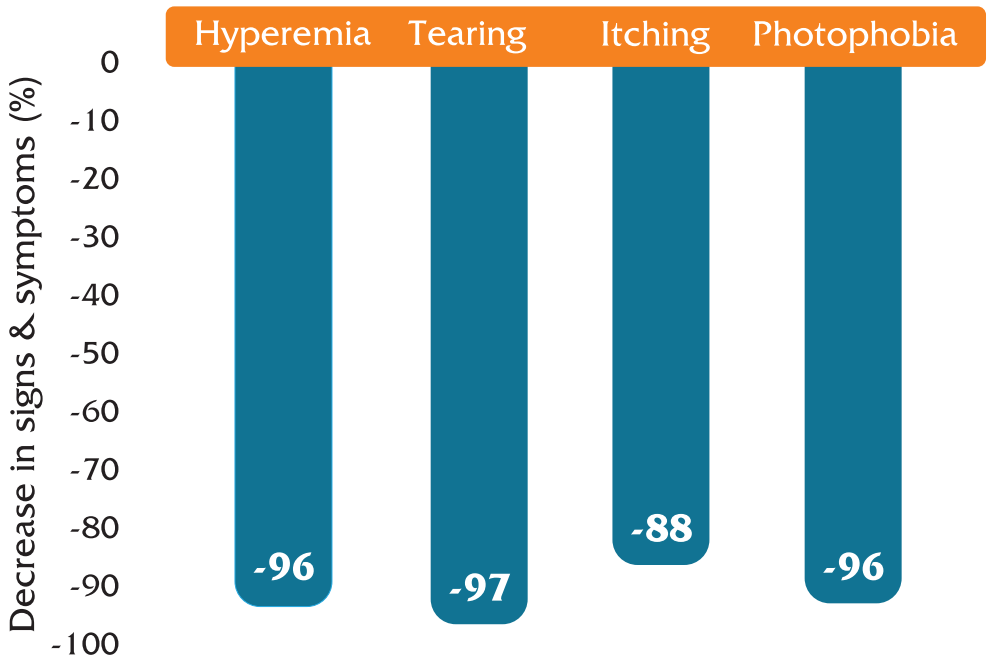
Springer Healthcare Education

In Allergic Conjunctivitis

Winolap/DS

(Olopatadine 0.1% / 0.2% Ophthalmic Solution)



- Effectively controls signs & symptoms of AC[1]
- Ensures minimal allergic manifestations

Win over allergy

Ref. : 1. A N Choudhary et.al. A Study on the thrrapeutic efficacy of Olopatadine Hydrochloride in the management of allergic conjunctivitis; Medicine Today; 2010; volume 22; number 01
AC: Allergic Conjunctivitis

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Contents

Ocular Allergy

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1

Allergic Diseases of the Eye

Brett Bielory, Leonard Bielory

Physicians in all specialties frequently encounter various forms of inflammatory diseases of the eye that present as red eyes in their general practice. However, the eye is rarely the only target for an immediate allergic-type response (less than 5 % of allergic patients). Typically, patients have other atopic manifestations that affect the nose (rhinitis), sinuses (sinusitis), lungs (asthma), and skin (urticaria or eczema). However, ocular signs and symptoms may be the initial and the most prominent feature of the entire allergic response that patients present to their physician as reported in 2014 in the AIRS study.

The prevalence of allergies ranges as high as 30–50 % of the US population. Industrialized countries report greater allergy prevalence, starting with the original reports of vernal catarrh in Great Britain after the Industrial Revolution. Many theories abound about the increasing prevalence of allergies in the United States, such as climate change, increased industrialization, pollution, urbanization, and the hygiene theory. The combination of allergic nasal and ocular symptoms (rhinoconjunctivitis) is extremely common, but it is not clear whether the two are equal (i.e., whether rhinitis is more common than conjunctivitis or vice versa). In studies of allergic rhinitis, allergic conjunctivitis is reported in more than 75 % of patients and in more recent studies to be equal as a primary complaint to nasal symptoms, whereas asthma is reported in the range of 10–20 %.

The eye is probably the most common site for the development of allergic inflammation because it has no mechanical barrier to prevent the impact of airborne allergens on its surface. The nasal and ocular symptoms more appropriately called *conjunctivorhinitis* or *rhinoconjunctivitis* depending on which target organ symptom predominates may be perceived as a mere nuisance;

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their consequences can profoundly affect the patient's quality of life. Seasonal allergic rhinitis and conjunctivitis have been associated with headache and fatigue, impaired concentration and learning, loss of sleep, reduced productivity, somnolence, functional impairment, and increased occupational risks for accidents or injuries secondary to sedating oral antihistamine therapy, especially those sold over the counter. Patients with seasonal allergies appear to suffer equally from conjunctivitis symptoms as rhinitis symptoms. However, over 50 % of patients with rhinoconjunctivitis never appreciate the impact of their ocular symptoms until they receive specific targeted treatment to the ocular surface.

The Ocular Surface

The surface of the eye easily attracts many deposits such as allergens and other ocular irritants. These agents are concentrated in tears and can cause allergic conjunctivitis as well as toxic/irritant conjunctivitis. Overuse of vasoconstrictive agents used to alleviate allergic conjunctivitis can cause *conjunctivitis medicamentosa*. Uveitis, scleritis, or other systemic autoimmune disorders may also be a cause of red eye, but are also more commonly associated with complaints of pain. The effects of the allergic inflammatory response are mediated by the release of an array of mediators including histamine, leukotrienes, and neuropeptides.

Clinical Examination

The history and clinical examination provide clues for the clinician to refine their differential diagnoses for the patient suffering from chronic conjunctivitis commonly referred to as the "pinkeye" (Fig. 1). The clinical examination of the eyes for ocular allergy should include an examination of the periorbital tissue followed by the ocular surface. 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, and ptosis that 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, as are its amount, duration, location, and color. Differentiation between scleral and conjunctival injection must be made in the clinical examination that can be established upon instillation of phenylephrine 2 % drop to monitor presence of arterial blanching. Scleral injection (scleritis) tends to develop over several days and is associated with severe intraorbital ocular pain on motion. Conjunctivitis is associated with discomfort, but not *pain*. Scleritis commonly develops in patients with systemic autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and Wegener's granulomatosis, but it has been known to occur in the absence of any other obvious clinical disorders. Ciliary flush is another form of ocular injection described as a ring of erythema around the limbal junction of the cornea that is a clinical sign for intraocular inflammation and uveitis. The bulbar and tarsal conjunctival surface should also be closely examined for the presence of inflammatory follicles or papillae. Follicles may be distinguished as grayish, clear, or yellow bumps, varying in size from

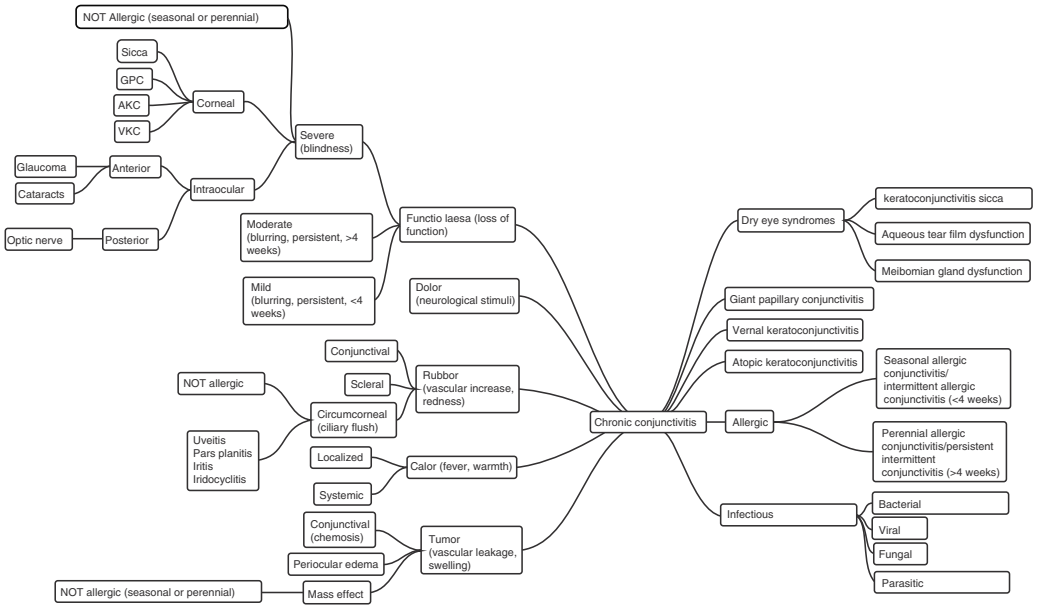

Fig. 1: The differential diagnosis of conjunctivitis is based on etiology of the underlying inflammatory response (i.e., infectious, allergic, or autoimmune); the signs and symptoms of inflammation (rubor, calor, dolor, tumor, functio laesa) can assist in honing of the etiology and provide a more focus approach to treatment.

pinpoint to 2 mm in diameter with conjunctival vessels on their surface, whereas papillae contain a centrally located tuft of blood vessels. The cornea is rarely involved in acute forms of allergic conjunctivitis, whereas in the chronic forms of ocular allergy, such as vernal keratoconjunctivitis and atopic keratoconjunctivitis, the prefix kerato- reflects the common involvement of the cornea.

The optimum examination of the cornea is with the slit-lamp biomicroscope. However, many important clinical features may be seen with the naked eye or a handheld direct ophthalmoscope. The direct ophthalmoscope can provide the desired magnification by "plus" (convex) and "minus" (concave) lenses. The cobalt blue filter on the new handheld ophthalmoscopic heads assists in highlighting anatomic anomalies affecting the cornea or the conjunctiva, which has 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 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 normally invisible to the naked eye, but when inflamed this area becomes visible as a pale or pink swelling. Some case reports of limbal allergy exist. Conjunctival erythema can be measured objectively with a spectroradiometer, which measures the chromaticity of reflected light. Erythema, edema, and itching can be graded on a Likert scale, e.g., 0–4 scale. Edema can be measured objectively by using a fractional millimeter reticle in the eyepiece of a slit-lamp microscope. Discrete swellings with small white eosinophilic collections at the limbal border (Horner-Trantas dots) are indicative of degenerating cellular debris,

which are commonly seen in chronic forms of conjunctivitis. In addition, because the eye has thin layers of tissue surrounding it, there is an increased tendency to develop secondary infections that can further complicate the clinical presentation. Direct signs of inflammation such as conjunctival injection and edema significantly correlate with the severity of corneal complications. The height of papillae and the amount of mucous discharge do not necessarily correlate with the severity of corneal complications, but appear to be associated with location of corneal changes.

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. Inflammation of the conjunctiva rather than mechanical factors plays a greater role in the formation of corneal damage in chronic allergic eye disease. These conditions may be considered part of an immunologic spectrum that affects the anterior surface of the eye with a variety of disorders that may overlap and include seasonal and perennial allergic conjunctivitis, vernal and atopic keratoconjunctivitis (VKC, AKC), and giant papillary conjunctivitis (GPC). In addition, tear film dysfunction, also known as dry eye syndrome, commonly complicates ocular allergy and its treatments, especially as the age of the patient increases. Tear film dysfunction is also included in the spectrum of IgE-mast cell hypersensitivity conditions as it commonly overlaps with mast cell and cell-mediated disorders, but involve different mechanisms, cytokines, and cellular population. For example, mast cell degranulation, histamine release, and eosinophils play key roles in the common forms of seasonal and perennial conjunctivitis associated with a TH2 lymphocyte cell population. By contrast, AKC and VKC are characterized by more chronic, inflammatory cellular infiltrates, primarily composed of CD8+ lymphocytes with minimal interplay with mast cells and note changes in cytokine production such as TH1 lymphocyte cytokine, gamma-interferon (IFN). Tear film dysfunction, which is a CD4+-mediated disorder, commonly complicates ocular allergy syndromes.

Mast cell mediators, such as histamine, tryptase, leukotrienes, prostaglandins, and cytokines in the tear fluid, have diverse and overlapping biologic effects, all of which contribute to the characteristic itching, redness, watering, and mucous discharge associated with both acute and chronic allergic eye disease. Histamine alone is involved in 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 that is derived from the human conjunctival tissue that contains approximately 10,000 mast cells per cubic millimeter. 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. Most ocular allergic reactions appear to be mediated through the effects on a combination of histamine receptors (H1, H2, and potentially H4) as it can induce changes in the eye similar to those seen in other parts of the body.

These include capillary dilation leading to conjunctival redness, increased vascular permeability leading to chemosis, and smooth muscle contraction.

In more severe chronic allergy-related conditions, T cells are the key cellular players in ocular surface impairment. Two predominant inflammatory pathways are differentiated by the CD4+ and CD8+ 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 CD4+ and CD8+ activations were found in AKC. However, evidence for Th1 involvement has been noted in the more severe form with expression of gamma-IFN. Historically, studies using conjunctival biopsies or brush cytology specimens have demonstrated increased CD8+ cytokines in SAC: IL-4 and IL-13 and an increasing awareness for the potential involvement of IL-9. In addition, it is not rare for a patient treated for typical seasonal allergic conjunctivitis also to develop dry eye, tear film disturbance, meibomian dysfunction, tear film hyperosmolarity, adverse effects from the repeated use of toxic preservative-containing topical drugs, or contact cell-mediated conjunctival or eyelid hypersensitivity, conditions linked to the CD4+ cascade.

The four major ocular allergies, SAC/PAC, AKC, VKC, and GPC, exhibit increased levels of conjunctival cell adhesion molecules (CAMs) and eosinophils in conjunctival scrapings. The tears of patients challenged with high-dose allergens have been found to exhibit eosinophil cationic protein (ECP), which correlates with their symptomatology. Eosinophils found in the conjunctiva of patients with VKC are considered to be the "histologic hallmark" of the disease. It has been suggested that because the quantity of eosinophils correlates highly with the allergic signs and symptoms of VKC patients, their clinical status could be represented by tear ECP levels, which also correlate highly with the number of eosinophils. A large amount of major basic protein (MBP) has also been found in the tears of patients with VKC associated with the corneal ulcerations. In vitro experiments have shown that MBP exhibits corneal toxicity and retards wound repair in corneal epithelial cells. The number of eosinophils has also correlated with the severity of AKC with higher levels in patients with corneal erosions and ulcers compared to those with superficial keratopathy, which suggests that eotaxin causes corneal damage in AKC. Interestingly, patients with GPC have higher levels of eosinophilic infiltrate than both VKC and AKC; however, tear ECP levels in these patients are significantly lower than tears from patients with VKC and AKC. Neutrophils and neutrophil-derived mediators (neutrophil myeloperoxidase, elastase) are also increased in the tears of both AKC and VKC. However, IL-8, which is a neutrophil chemoattractant, is increased in tears from AKC but not in tears from VKC. IL-8 still plays a role in the pathogenesis of VKC, but the response of IL-8 is enhanced in AKC. Colonization of *Staphylococcus aureus* is a possible explanation for the enhancement of IL-8 in AKC. Peptidoglycan from *S. aureus* has been shown to stimulate IL-8 release from conjunctival epithelial cells and is enhanced in the presence of gamma-IFN. AKC is a manifestation of atopic dermatitis, and 67 % of atopic dermatitis patients have colonization with *S. aureus* within conjunctival sacs and eyelid margins.

Acute Allergic Conjunctivitis

Allergic conjunctivitis (AC) is a bilateral, self-limiting conjunctival inflammatory process. AC occurs in sensitized patients with no sex difference. The most common target organ for the mast cell IgE hypersensitivity-mediated reaction may actually be the eye. The allergic reaction in allergic conjunctivitis is caused by direct exposure of the ocular mucosal surfaces to environmental allergens such as pollens from trees, grasses, and weeds. These allergens interact 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 "conjunctivorhinitis" in the United States. With the recent increase of ragweed growth in Europe and the Middle East, ragweed appears to contribute to approximately 75 % of all cases of hay fever with prevalence varying among different age groups in various regions of the world. Early allergy testing revealed Timothy grass as one of the most potent ocular allergy-inducing allergens. There are two forms of AC seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), which are defined by whether the inflammation is associated with seasonal change (spring, fall) or perennially. Both entities share the same inflammatory symptoms. However, seasonal allergic conjunctivitis is related to atmospheric pollens such as grass, trees, and ragweed that appear during specific seasons, whereas perennial allergic conjunctivitis is related to animal dander, dust mites, or other allergens that are present in the environment continuously. A major distinguishing feature between AC and VKC/AKC is that AC is self-limited, not causing ocular or visual damage, while VKC and AKC can involve the cornea causing visual damage. Common conjunctival symptoms in AC include itching, tearing, and often burning. Although involvement of the cornea is rare; blurring of vision can occur. 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, becoming stringy in the chronic form. Ocular signs are typically mild; the conjunctiva frequently takes on a pale, boggy appearance that evolves into diffuse areas of papillae (small vascularized nodules), which tend to be most prominent on the superior palpebral conjunctiva. Occasionally, dark circles beneath the eyes (allergic shiners) are present, which are formed as a result of localized venous congestion. The ocular reaction seen in both seasonal AC and perennial AC often resolves quickly when the offending allergen is removed. A detailed history from the patient or family members can expedite the diagnosis of AC. A family history of atopy or hay fever is often elicited. Both SAC and PAC are treated with agents that combine both antihistamines and mast cell stabilizers. The rationale for the dual treatment is rapid symptomatic relief with the antihistamine and long-term disease-modifying benefits with mast cell stabilization.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is defined as a chronic allergic disorder of the conjunctiva mediated by mast cells and lymphocytes. There are three major forms of the disease: palpebral, limbal, and mixed. VKC is most prevalent in the spring (vernal). Symptoms include intense bilateral ocular pruritus, which is often induced by nonallergic stimuli: dust, wind, bright light,

hot weather, or physical exertion. VKC is more common in prepubescent boys; however, after puberty, the sexes are equally afflicted with progressive dissipation of symptoms through the third decade of life. The most remarkable physical finding in VKC is giant papillae present on the tarsal conjunctiva, measuring 7–8 mm in diameter of the upper tarsal plate, which result in the cobblestone appearance seen on examination. Horner points and Horner-Trantas dots, thin, copious, mild-white fibrinous secretions or yellowish-white points, may be present. Other physical findings include an extra eyelid crease (Dennie's line), corneal shield ulcers, or a pseudomembrane formation of the upper lid when everted and exposed to heat (Maxwell-Lyon sign). VKC is most often bilateral; however, 5 % of patients are affected more in one eye with severe cases causing blindness. The use of a cobalt blue light with the application of topical fluorescein dye can reveal diffuse areas of punctate corneal epithelial defects. These defects may progress into shield ulcers, which are areas of desquamation of epithelial cells caused by the release of major basic protein from eosinophilic infiltrate. More than 50 % of patients with VKC do not report a history of atopic disease and do not show IgE sensitization, which proposes that VKC is not entirely mediated by IgE, but recent studies suggest increased local ocular sensitization to aeroallergens. VKC is characterized by infiltration of the conjunctiva by eosinophils, basophils, mast cells, CD4+ Th2, monocytes, macrophages, dendritic cells, plasma cells, and B lymphocytes organized as small lymphoid follicles. It is these infiltrates that cause the corneal involvement, photophobia, foreign body sensation, and lacrimation that are present in VKC. They serve not only as an anatomic barrier, but they are also capable of synthesizing chemokines, most notably eotaxin, a potent CC chemokine, and RANTES (regulated on activation, normal T cell expressed and secreted) that can modulate inflammation. It has been noted that tarsal and bulbar conjunctival biopsy specimens with VKC have stained positive for estrogen and progesterone receptors, thus implicating that eosinophilic infiltrate in VKC may be influenced by these hormones.

The treatment of VKC includes cold compress, natural tears, avoidance of any known triggers, topical antihistamines, topical mast cell stabilizers, and periodic use of corticosteroids for acute exacerbations. The use of FK-506 has also shown favorable responses in VKC. In comparison to 2 % cyclosporine, FK-506 was shown to decrease symptoms of VKC up to 26 % from baseline, and FK-506 was not associated with the persistent burning sensation described with 2 % cyclosporine. Montelukast treatment of asthma patients with coexisting VKC resulted in decreased hyperemia, secretion, chemosis, burning, tearing, and photophobia. The benefits persisted 15 days after discontinuation of treatment, thus suggesting a role for leukotrienes in VKC with coexisting asthma. The plaques associated with VKC that can be caused by eosinophilic infiltrate may be removed by superficial keratectomy with possible reepithelialization of the cornea. Potential future treatments for VKC are targeting immunobiologicals targeting cytokine receptor antagonists to inhibit inflammation of the conjunctiva.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is a bilateral, chronic mast cell and lymphocyte-mediated allergic disorder involving the conjunctiva, eyelids, and periorbital tissue often associated with

a family history of atopy, eczema, and asthma. Approximately 15–40 % of patients with atopic dermatitis also have ocular involvement due to AKC. Patients often have atopic dermatitis and/or eczema from childhood and develop the ocular symptoms of AKC later in life, but pediatric and adolescent cases do occur. Primary care physicians should expect to see approximately 25 % of their elderly patients who have eczema to develop some components of AKC. It more commonly presents in individuals older than 50 years. There is no racial or geographical preference. AKC can cause disabling symptoms including blindness when the cornea is involved. Ocular symptoms of AKC are similar to the cutaneous symptoms of eczema, including intense pruritus and edematous, coarse, and thickened eyelids. Severe AKC is associated with complications such as blepharoconjunctivitis, cataract, corneal disease, and ocular herpes simplex, rope-like mucus discharge, tylosis, and meibomian gland dysfunction. The symptoms of AKC commonly include itching, burning, and tearing that are more severe than those seen in allergic conjunctivitis or perennial allergic conjunctivitis. The symptoms of AKC also tend to be present throughout the year and are associated with seasonal exacerbations, especially in the winter and summer months. AKC can be exacerbated by other allergic triggers, e.g., animal dander, dust, and certain foods. The chronicity of AKC and corneal infiltration are due to T-cell involvement. However, unlike vernal keratoconjunctivitis, which has a T helper cell type 2 profile, AKC is associated with a mixture of both T helper cell types 1 and 2. Of note, mast cells and eosinophils are found in conjunctival epithelium of AKC patients but not in patients not afflicted with AKC. Ocular disease activity in AKC correlates with exacerbations and remissions of the dermatitis. AKC-associated cataracts occur in approximately 10 % of patients with the severe forms of atopic dermatitis but are especially prone to occur 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. AKC patients may also develop posterior polar-type cataracts due to the prolonged use of topical or oral corticosteroid therapy. A small percentage of patients with atopic dermatitis also develop keratoconus, a conical protrusion of the cornea caused by thinning of the stroma. Retinal detachment is increased in patients with AKC; however, it is also increased in patients with atopic dermatitis in general. An association has been found between exacerbations and specific microorganisms such as *S. aureus* and keratoconjunctivitis with specific IgE antibody to staphylococcal enterotoxin in tears of patients with VKC and AKC. Treatment for AKC involves corticosteroids, antihistamines, and mast cell stabilizers as well as treatment of any features of atopic dermatitis. The clinician should use antihistamines with caution in elderly patients because they cause increase drying of the conjunctival surface.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis (GPC) is not a true ocular allergy, but rather the result of chronic mechanical irritation. Many of the features of GPC mimic other ocular hypersensitivity syndromes. GPC is even noted to have an increase in symptoms during the spring pollen season. Therefore, it is included in the differential diagnosis of ocular allergy. GPC has an association with extended-wear soft contact lenses and other foreign bodies, such as suture materials and

ocular prosthetics. Lens-induced papillary conjunctivitis may develop 3 weeks after using soft contact lenses. Patients who wear rigid or hard contacts may develop symptoms of GPC within 14 months from the onset of wear. The pathogenesis of GPC is due to mechanical trauma followed by repeat immunologic presentation of foreign antigens, most often surface deposits or environmental agents. The signs of GPC include a white or clear exudate on awakening, which chronically becomes thick and stringy. The patient may develop papillary hypertrophy (cobblestoning), especially in the tarsal conjunctiva of the upper lid, which is more common in patients that wear soft contact lenses than hard contact lenses, 5–10 % versus 4 %, respectively. The contact lens polymer preservatives, such as thimerosal, and proteinaceous deposits on the surface of the lens have all been implicated in the cause of GPC. Common symptoms include intense itching, decreased tolerance to contact lens wear, blurred vision, conjunctival injection, and increased mucus production. Patients wearing contact lenses produce local antigenic factors that can trigger eotaxin production, which acts as a chemoattractant for eosinophils. The eosinophils then release major basic protein and toxic mediators causing the papilla formation. The treatment for GPC involves corticosteroids, antihistamines, 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. GPC usually resolves when the patient stops wearing contact lenses or when the foreign body is removed from the eye.

Dry Eye Syndrome (Tear Film Dysfunction)

Dry eye syndrome (DES), also known as tear film dysfunction, develops from decreased tear production, increased tear evaporation, increased tear osmolarity, or an abnormality in specific components of the aqueous, lipid, or mucin layers that compose the tear film. DES is associated with atopy, female gender, and chronic medication use, including hormone replacement therapy. DES affects over 14 million people in the United States. Symptoms of DES are typically vague and include foreign body sensation, easily fatigued eyes, dryness, burning, itching, ocular pain photophobia, and blurry vision. Many symptoms overlap other forms of ocular allergy. Upon the onset of DES, patients complain of a mildly injected eye with excessive mucus production and gritty sensation, as compared with the itching and burning feeling that many patients report with allergy-associated histamine release onto the conjunctiva. Symptoms tend to be worse late in the day, after prolonged use of the eyes or exposure to adverse environmental conditions. DES has significant economic implications, including costs associated with increased health-care utilization, missed school and work, and leisure and quality-of-life issues. Although dry eye may occur as a distinct disorder resulting from intrinsic tear pathology, it is more frequently associated with other ocular and systemic disorders, including ocular allergy, chronic blepharitis, fifth or seventh nerve palsies, vitamin A deficiency, pemphigoid, and trauma. DES is a frequent confounding disorder that may complicate ocular allergic disease with several overlapping signs and symptoms, such as tearing, injection, and exacerbation. As the cornea becomes involved, the symptom progress to include photophobia as well as more scratchy and painful sensations. DES and ocular allergy conditions are not exclusive; as patients age, the likelihood of tear film dysfunction complicating

ocular allergy increases. A more systemic form of DES, associated with systemic immune diseases such as Sjögren's syndrome, rheumatoid arthritis, and HIV infection, is commonly known as keratoconjunctivitis sicca and can be a symptom in postmenopausal women. The most common cause of DES is associated with the use of anticholinergic medications, which decrease lacrimation. Drugs with antimuscarinic properties include the first-generation antihistamines, phenothiazines, tricyclic antidepressants, atropine, and scopolamine and even newer antihistamine agents, such as loratadine and cetirizine.

Other agents associated with a sicca syndrome include the retinoids, β-blockers, and chemotherapeutic agents. Tear film dysfunction is also associated with several pharmacologic agents, including antihistamines, anticholinergics, and certain psychotropic agents. Patients often note that their symptoms are exacerbated in the winter when heating systems decrease the relative humidity in the household to less than 25 %. The Schirmer's test is used to diagnose DES. The test demonstrates decreased tearing (0–1 mm of wetting at 1 min and 2–3 mm at 5 min). Normal values for the Schirmer's test are more than 4 mm at 1 min and 10 mm at 5 min. Tear osmolarity measurements also provide a qualitative assessment of tears as increased salt concentrations (increased osmolarity) correspond with severity of DES. Treatments for DES include addressing the underlying pathology, discontinuing the offending drug (if possible), and making generous use of artificial tears or ocular lubricants. Topical cyclosporine (Restasis®) has been approved by the US Food and Drug Administration for the treatment of DES. For severe symptoms, insertion of punctual plugs may be indicated.

Contact Dermatitis of the Eyelids

Contact dermatoconjunctivitis is a delayed type of lymphocytic hypersensitivity reaction involving the eyelids and the conjunctiva as opposed to an ocular allergy, which activates the IgE mast cell. The eyelid skin is extremely thin, soft, and pliable and is capable of developing significant swelling and redness with minor degrees of inflammation or irritation. As a result, the patient frequently seeks medical attention for a cutaneous reaction that elsewhere on the skin would normally be less of a concern. Two predominant forms of contact dermatitis are attributed to cosmetics of the eye. These include contact dermatoconjunctivitis and irritant (toxic) contact dermatitis. Contact dermatoconjunctivitis is commonly associated with cosmetics to the hair, face, or fingernails (e.g., hair dye, nail polish) or with topical ocular medications (e.g., neomycin). Certain preservatives, such as thimerosal, which is in contact lens cleaning solutions, and benzalkonium chloride, which is in many topical ocular therapeutic agents, have both been shown by patch testing to be causes of contact dermatitis. The most common complaints associated with contact dermatitis are stinging, burning, and itching of the eyes and lids. The symptoms are subjective and are usually transitory if there is no evidence of objective signs of irritation. The patch test can assist in pinpointing the causative antigen, but interpretation of patch test results may be difficult. Patch testing is also associated with high false-positive reactions when associated with irritants. Patch tests performed with patients' own topical ophthalmic products are often negative. However, pretreatment with sodium lauryl sulfate increases patch test sensitivity.

Blepharoconjunctivitis

Blepharitis is a primary inflammation of the eyelid margins that is most often misdiagnosed as an ocular allergy because it commonly causes conjunctivitis secondary to a blepharitis. The most common causes are seborrhea and infection; the most common organism is *S. aureus*. The signs of staphylococcal blepharitis are dilated blood vessels, erythema, scales, collarettes of exudative material around the eyelash bases, and foamy exudates in the tear film. Antigenic products play the primary role in the induction of chronic eczema of the eyelid margins. Certain lipophilic organisms such as *Malassezia* yeast may be highly antigenic and induce chronic inflammatory reactions. Even a form of mite (Demodex) has been associated with refractory cases of blepharoconjunctivitis where the mite burrows into the rim of the eyelid. Symptoms include persistent burning, itching, tearing, and a feeling of dryness. Blepharitis differs from dry eye syndrome in that the symptoms of blepharitis are more persistent in the morning than the evening and the symptoms of dry eye syndrome are more persistent in the evening. Crusted exudate develops with blepharitis that may prevent the eye from opening when the patient awakens in the morning. Blepharitis may be controlled with proper eyelid hygiene: using detergents (e.g., nonstinging baby shampoos) and steroid ointments applied to the lid margin with a cotton tip applicator that is used to loosen scales and exudate. Tea tree oil has been used in the treatment of Demodex infestation.

Ocular Allergy Treatment

A variety of treatment approaches have been used to manage allergic symptoms, foremost among them the avoidance of triggering allergens. In addition, pharmacotherapies with antihistamines, decongestants, nasal corticosteroids, mast cell stabilizers, and anticholinergics have all proven effective, as has immunotherapy. Ocular allergy treatment should be considered in a stepwise approach (Fig. 2). Primary treatment of any allergy, including ocular allergy, focuses on the avoidance of allergens. This strategy primarily involves the use of environmental interventions, from removal of the offending allergen source to a change of occupational venue. However, this is not often practical because it could mean attempting to avoid the outdoors or family pets. Lubrication is a form of avoidance, in that it has a dilutional effect on allergens and released mediators that interact with the conjunctival surface. Cold compresses provide considerable symptomatic relief, especially from ocular pruritus. All ocular medications should be refrigerated to provide additional subjective relief when applied to the conjunctival surface. Systemic agents can cause ocular drying that can alter the ocular tear film's ability to act as a protective barrier against external matter such as airborne allergens. This decreased tear production may decrease the eye's ability to wash allergens from the ocular surface, allowing them to remain there longer and possibly worsen allergic signs and symptoms. Secondary treatment regimens include the symptomatic use of topical agents, as well as oral decongestants, antihistamines, mast cell-stabilizing agents, and antiinflammatory agents. Topical decongestants primarily act as vasoconstrictors, which are highly effective in reducing the erythema and are widely used in combination with topical antihistamines. Adverse effects of topical vasoconstrictors include burning and stinging on instillation, mydriasis,

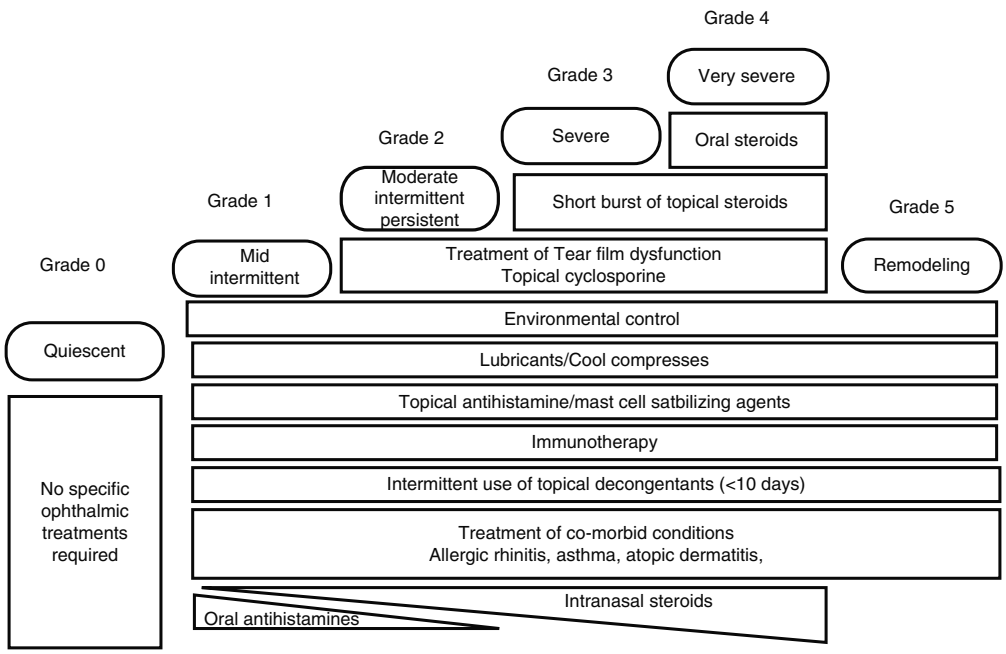

Fig. 2: The treatment of ocular allergy should proceed in a stepwise approach in concert of the treatment of other comorbid allergic disorders (e.g., allergic rhinitis, allergic urticaria, atopic dermatitis, tear film abnormalities/dry eye syndromes). Environmental control remains an important underpinning of all treatments of ocular that is complemented with nonpharmacologic treatments such as lubricants and cold compresses. Topical pharmacotherapy becomes the primary treatment when ocular symptoms predominate. The use of oral antihistamines should be limited to initial treatments as they may cause increased drying of the ocular surface in those that suffer from tear film insufficiency. Intranasal steroids improve mild symptoms of ocular allergy, but to be used when the patient has both nasal and ocular symptoms. Immunotherapy should be considered for those refractory to pharmacotherapy treatment.

especially in patients with lighter irises, and rebound hyperemia or conjunctivitis medicamentosa with chronic use. In the conjunctiva, H1 stimulation principally mediates the symptom of pruritus, as seen in various binding studies, whereas the H2 receptor has been inferred to be clinically involved in the vasodilation of the ocular allergic response. Although topical antihistamines may be used alone to treat AC, combined use of an antihistamine and a vasoconstricting agent is more effective than either agent alone.

As monotherapy, oral or systemic antihistamines are an excellent choice when attempting to control multiple early-phase and some late-phase allergic symptoms in the eyes, nose, and pharynx. Despite their efficacy in relief of allergic symptoms, systemic antihistamines may result in unwanted side effects, such as drowsiness and dry mouth. Newer, second-generation antihistamines are preferred to avoid the sedative and anticholinergic effects associated with first-generation agents. SAC and PAC are ideally treated with a combination of antihistamine and mast cell stabilizers. These combination therapies have the advantage of giving immediate symptomatic

relief via the antihistamine effect as well as having long-term modifying effects on the disease with mast cell stabilization.

When the allergic symptom or complaint is isolated, such as ocular pruritus, focused therapy with topical antihistaminic agents is often efficacious and clearly superior, either as monotherapy or in conjunction with an oral or nasal agent. Topical antihistaminic agents provide faster and better relief than systemic antihistamines. Topical antihistaminic agents also have a longer duration of action than other classes. However, their duration of action may not be as long as that of systemic agents. Some of these agents have been found to have merits as topical multiple action agents possessing unique properties, including HI-receptor antagonism, low antimuscarinic properties, and H2-receptor antagonism; these maximize the symptomatic treatment of seasonal AC and are now widely used as first-line pharmacotherapy for ocular allergy. Many of the selective Hl-receptor antagonists have also demonstrated impact on cytokines that have an impact on the ocular late-phase reaction seen in more than 50 % of patients and may explain the persistent qualities of the acute allergic ocular reaction. For example, some of these newer antihistamines can block intercellular adhesion molecule-1 (ICAM-1) expression in epithelial cells, effectively reducing inflammatory cell mucosal infiltration and cytokines including IL-4, IL-10, and IL-17.

The use of mast cell stabilizers such as cromolyn was originally approved for more severe forms of conjunctivitis (i.e., GPC, AKC, VKC), but many physicians have used it for the treatment of acute seasonal and perennial AC with an excellent safety record. Mast cell stabilizers inhibit degranulation and block the release of preformed mediators within the mast cell. For mast cell stabilizers to be effective, the mast cell has to be deactivated before the allergic reaction is triggered. However, mast cell stabilizers require a loading period and must be applied for several weeks before antigen exposure to fully decrease the allergic response. Compliance is important with the use of mast cell stabilizers because they require frequent, regular dosing. Some of the studies reflecting their clinical efficacy for seasonal and perennial AC found marginal efficacy when compared with placebo in clinical settings and some animal models. After many years of clinical use, the mechanisms of cromolyn are still unclear.

Ketorolac is a nonsteroidal antiinflammatory drug (NSAID) that inhibits the prostaglandin production involved in mediating ocular allergy. Ketorolac is indicated for itchiness associated with AC. Clinical studies have shown that topical NSAIDs significantly diminish the ocular itching and conjunctival hyperemia associated with seasonal antigen-induced AC and VKC. These agents, unlike topical corticosteroids, do not mask ocular infections, affect wound healing, increase intraocular pressure, or contribute to cataract formation. Some of the studies reflecting their clinical efficacy for seasonal and perennial AC showed marginal efficacy when compared with placebo in clinical settings and in some animal models. Ketorolac is associated with stinging on application that quickly dissipates.

Tertiary treatment of ocular allergy using more potent immunomodulatory properties such as steroids may be considered when topically administered medications, such as antihistamines, vasoconstrictors, or cromolyn sodium, are ineffective. However, the local administration of topical steroids may be associated with localized ocular complications, including increased intraocular pressure, viral infections, and cataract formation. Two modified steroids that are

topically applied, rimexolone and loteprednol, have recently been investigated for their efficacy in AC. Rimexolone is a derivative of prednisolone that is quickly inactivated in the anterior chamber. Loteprednol is another modified corticosteroid that is highly effective in the acute and prophylactic treatment of AC.

Immunotherapy has been used for the primary treatment of allergies, once known as spring catarrh before the discovery of antihistamines and other pharmacologic agents. In fact, in the original report on allergy immunotherapy in the early 1900s, it was used to "measure the patient's resistance during experiments of pollen extracts to excite a *conjunctival* reaction." Immunotherapy primarily involves the subcutaneous immunotherapy (SCIT) application of the suspected proteins in various formulations, but recently has expanded into sublingual immunotherapy (SLIT) administration to a limited array of specific allergens.

Although initial SCIT studies did not specifically address ocular symptoms, more recent clinical studies have started to identify improvement in ocular signs and symptoms in a separate domain of assessment outcomes. Additional physiologic studies involving SCIT have demonstrated a logarithmic increase (10- to 100-fold) in the tolerance to the allergen in the conjunctival provocation test or improvement of ocular symptoms. Interestingly, when specific allergen immunotherapy was instituted in adults and children with multiple allergies, the treatment was both effective and specific to the allergens in their season. When increasing doses of specific allergen or allergoid immunotherapy are used, there is progressive control of allergic inflammation. Allergoid immunotherapy induces immunomodulation with fewer doses of treatment (e.g., four allergoid doses versus weekly or monthly allergen doses over the course of a year). Subcutaneous administrations of allergen solutions are not convenient for all patients. SLIT has also been attempted in the treatment of seasonal and perennial rhinitis with a statistical decrease in ocular symptoms. Some produce no changes in the rhinitis symptoms, suggesting that ocular symptoms may be more sensitive to treatment with allergen immunotherapy. SLIT requires daily administration months in advance of the patient's specific allergy season.

Experimentally, AC has been suppressed by the oral administration of the offending allergen in animal models, with the concomitant decrease in the development of allergen-specific IgE. Recent experimental studies on the use of sublingual immunotherapy have also shown statistical improvement in the nasal and ocular symptom scores, which are also associated with an increase in the threshold dose for the conjunctival allergen provocation tests. Experimental topical application of allergen or immunostimulatory sequence oligodeoxynucleotides has predominantly shown a decrease in the late-phase response. Future treatments for ocular allergy may concentrate on various immunobiologicals that interfere with the ongoing allergic inflammation response as well as targeting specific targets such as eosinophils with inhibition of IL-5, CCR-3, and other cytokines.

Vasomotor Conjunctivitis or Perennial Chronic Conjunctivitis

The identification of vasomotor conjunctivitis (VMC) or perennial chronic conjunctivitis (PerCC) is not commonly included in the differential diagnosis of allergic conjunctivitis, although it may

occur in as many as 25 % of patients complaining of ocular symptoms that are commonly confused with allergy. These patients are by definition skin test negative, but they react to environmental stimulants such as weather, pollution, and/or wind. These disorders need to be better defined, categorized, and classified to determine the best treatment modalities as it may represent a form of tear film dysfunction and may benefit by the treatment trial of DES.

Conclusion

The prevalence of ocular allergy continues to be clearly underappreciated; it has been an underdiagnosed and undertreated area in primary care medicine. The ocular symptoms associated with the most common ocular allergy conditions, such as SAC and PAC, are intricately linked to allergic rhinitis in more than 90 % of cases. The emergence of new medications and forms of immunotherapy (e.g., subcutaneous allergoid, sublingual immunotherapy) for the specific treatment of ocular symptoms offers a new field for improved patient care by the primary and subspecialty healthcare providers and with further research into the immunobiologicals may offer sight-saving treatments for patient suffering from the more chronic forms of ocular allergy that have corneal involvement.

Evidence-Based Medicine

One of new areas of research in allergy is the examination of epithelial integrity in the promotion of the ongoing allergic inflammation. In one of few head to head studies of topical agents comparing topical antihistamines that are commonly prescribed in the stepwise approach in the treatment of ocular allergy, two antihistamines, olopatadine and alcaftadine, were compared for their ability to modify epithelial cell changes associated with allergic conjunctivitis at time points selected to reflect acute (15 min) and late-phase (24 h) reactions. Using an animal with similar conjunctival allergen challenge for eosinophil numbers and for tight junctional protein expression, Dr. Ono reported that the two agents were similarly equivalent for control of the acute phase, but alcaftadine-treated animals had significantly lower conjunctival eosinophil infiltration than either controls or olopatadine-treated animals. Allergen challenge caused a significant decrease in expression of the junctional protein, ZO-1, and this decrease was prevented by alcaftadine but not by olopatadine, suggesting that alcaftadine may have therapeutic properties beyond its antihistamine action in its ability to reduce conjunctival eosinophil recruitment and a protective effect on epithelial tight junction protein expression.

One also needs to maintain perspective of the emerging pipeline for the treatment of anterior inflammatory disorders that are related including allergic conjunctivitis (AC) and dry eye syndrome (DES) of the novel techniques and molecular entities. Nye *et al.* reported on the potential use of intralymphatic immunotherapy, CpG oligonucleotides, N-acetylaspartylglutamate, resolvins (omega-3 fatty acids), lymphocyte function-associated antigen-1 (LFA-1) antagonist, chlorogenic acid, and other potential agents as well as updated various agents undergoing trials.

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2

Corneal Diseases in Children: Allergic Diseases

Andrea Cruzat, Kathryn Colby

Allergic Conjunctivitis: Seasonal and Perennial

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most common form of ocular allergies, affecting about 15–20% of the population (Wong *et al.* 2014). SAC is more prevalent than PAC. The onset of symptoms is seasonally related to specific circulating aeroallergens. The difference between seasonal and perennial allergic conjunctivitis is the specific allergens to which the patient is allergic. SAC is caused by airborne pollens during spring and summer (most commonly ragweed and grass pollen) while PAC is caused by perennial allergens such as animal dander, dust mites, mold, air pollutants, and feathers. Despite this difference, 79% of children with perennial allergic conjunctivitis commonly experience seasonal exacerbations of symptoms (Bielory 2000; Abelson and Granet 2006).

Symptoms and Signs

The cardinal symptom of allergic conjunctivitis is ocular pruritus. Watery discharge and milky or pale pink conjunctiva with vascular congestion (mild to moderate hyperemia) that may progress to swelling and conjunctival follicles may also occur. A white exudate may form during the acute state that becomes stringy in the chronic form. Palpebral edema can be mild to moderate, accompanied by venous congestion that gives it a dark appearance known as allergic dark circles. A lower lid crease (the so-called Dennie–Morgan line) may develop. Corneal involvement is rare (Friedlaender 2011). Acute chemosis (an excessive edema of the bulbar conjunctiva) may

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occasionally occur. In some cases a fine conjunctival follicular reaction or papillary hypertrophy along the tarsal conjunctival surface may also be seen.

Proper diagnosis is usually made clinically based on history and physical examination, with ocular itching the most common and important symptom. Most patients also have history of atopy with symptoms of allergic rhinitis (65–70%) (Takamura *et al.* 2011). Other frequent co-morbidities are asthma and eczema (Gradman and Wolthers 2006).

Pathogenesis

Seasonal and perennial allergic conjunctivitis are type 1 hypersensitivity reactions. Allergic conjunctivitis is caused by an allergen-induced inflammatory response in which allergens interact with IgE antibodies bound to the surface of sensitized conjunctival mast cells. Degranulation of mast cells induces enhanced tear levels of histamine, tryptase, prostaglandins, and leukotrienes that induce the symptoms of allergic conjunctivitis. This immediate or *early response* lasts clinically 20–30 min (La Rosa *et al.* 2013). Mediators released during mast cell degranulation initiate the recruitment of inflammatory cells including neutrophils, basophils, eosinophils, and T lymphocytes in the conjunctival mucosa. This leads to the ocular *late phase reaction* that occurs 4–6 h later and the release of T helper 2 type cytokines (interleukin [IL]-4, IL-5, IL-6 and IL-13) (Leonardi *et al.* 2007). The presence of specific IgE antibodies to seasonal or perennial allergens can be documented in almost all cases, and this test can be used for a definite diagnosis if in doubt (Bonini 2004). Tear fluid from SAC patients has been found to contain a small amount of eosinophils and histamine but elevated levels of IgE (Bielory 2000). Interestingly, 78% of PAC patients had demonstrated tear-specific IgE for house dust, whereas no SAC patients had measurable levels of IgE specific for house dust in tears (Bielory 2000). Histamine sensitivity has been noted to be different between normal subjects and atopic patients. Atopic patients require lower doses of histamine to cause symptoms than normal subjects (Bielory 2000). Allergic conjunctivitis is characterized histologically by infiltration of the conjunctiva with inflammatory cells, including neutrophils, eosinophils, lymphocytes, and macrophages (Bielory 2000).

Atopic Keratoconjunctivitis (AKC)

Atopic keratoconjunctivitis is a bilateral chronic inflammatory disorder that involves recurrent episodes of severe inflammation of the conjunctiva and eyelids, which can secondarily affect the cornea. More than 95% of AKC patients also have eczema and 87% have history of asthma (Bielory 2000). AKC typically begins in the late teens and may persist until the fourth or fifth decade of life (Bielory 2000).

Symptoms and Signs

Atopic keratoconjunctivitis patients tend to be older than children with SAC and present with disabling symptoms most commonly involving the lower tarsal conjunctiva. Symptoms include

ocular itching year round, blepharospasm, blurred vision, burning, tearing, photophobia, eye pain, and early-morning mucous discharge. Seasonal exacerbations have been reported to be more marked in the winter or summer months and after exposure to animal dander, dust, and certain foods (Foster and Calonge 1990).

Clinical exam may reveal eyelid eczema with scaling dermatitis with a fine sandpaper-like texture, loss of eyelashes or eyebrows (madarosis), and lateral canthus ulceration. The eczema around the eyes involves the periorbital skin and cheeks. Erythema, dry scales, Dennie–Morgan lines, and allergic shiners (darkness and swelling underneath the eyes) may occur. Secondary staphylococcal blepharitis is common. Corneal findings such as punctate epithelial keratopathy (Fig. 1), Horner's points or Trantas dots may also be present. Mild or severe conjunctival injection or chemosis and lower tarsal follicles or papillae may be seen (Abelson and Granet 2006; Bielory and Bielory 2010). The conjunctiva is edematous and may eventually manifest subepithelial fibrosis, fornix shortening, scarring, or symblepharon.

Complications can be severe and vision-threatening including corneal epithelial defects, keratitis, corneal scarring, and keratoconus. Atopic cataracts that are typically anterior and shield-like, but may be nuclear, cortical and even posterior subcapsular develop in 8–12% of affected patients (Bielory 2000). The use of corticosteroid therapy may also contribute to cataract development. Lichenification of the eyelid skin may cause cicatricial ectropion and lagophthalmos (Abelson and Granet 2006). Eczematous lesions may be found not only on the eyelids but also in any place of the body. Skin lesions are red and elevated in the antecubital or popliteal regions and are itchy. Physical exam findings are similar or overlap between vernal and atopic keratoconjunctivitis; however, VKC usually resolves by age 20 years, whereas AKC can persist throughout life and involves the eyelids (Friedlaender 2011). Approximately 45% of patients with AKC are skin test or allergosorbent test negative to common allergens (La Rosa *et al.* 2013). Other unusual

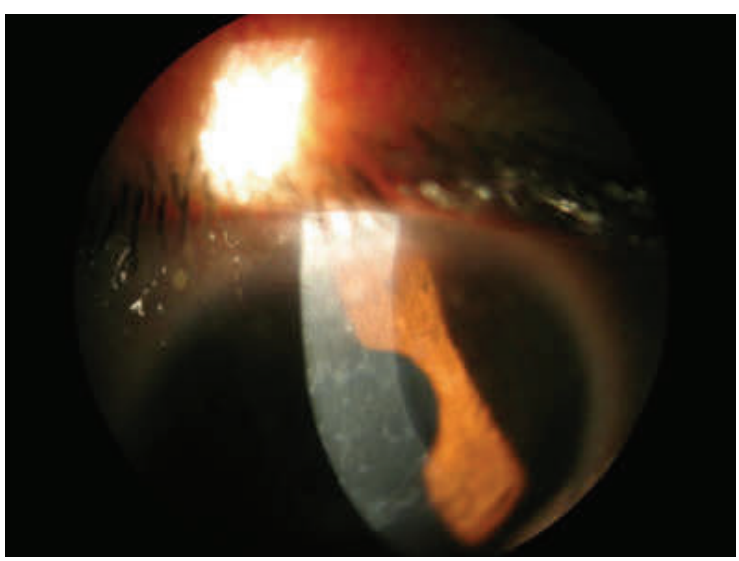

Fig. 1: Epithelial keratopathy in atopic keratoconjunctivitis.

complications include retinal detachment and a higher incidence of infections with herpes simplex keratitis and staphylococcus (Tuft *et al.* 1992; Bielory 2000). AKC is a clinical diagnosis; the history of systemic atopy and the perennial nature aids in distinguishing this from other forms of allergic conjunctivitis. Testing blood levels of histamine and increased total IgE antibodies in serum and lacrimal fluid and positive results of the serum antigen specific IgE antibody can be used as confirmatory tests of suspected disease (Takamura *et al.* 2011).

Pathogenesis

The pathophysiology of AKC involves both a type 1 hypersensitivity response with a chronic degranulation of mast cells mediated by IgE and a hypersensitivity type 4 response mediated by Th1- and Th2-lymphocyte derived cytokines (La Rosa *et al.* 2013). The T cell inflammatory response is confirmed by elevated systemic levels of IL-4 and IL-5 in atopic individuals (Jenmalm *et al.* 2001). The histopathologic findings of AKC include a mixture of mast cell, eosinophil, and lymphocyte infiltration into the conjunctival epithelium with both Th1 and Th2 interactions (Trocme and Sra 2002; Leonardi *et al.* 2007). Patients with atopic dermatitis and rhinoconjunctivitis commonly have elevated IgE and histamine levels in tears (Trocme and Sra 2002).

Vernal Keratoconjunctivitis (VKC)

Vernal keratoconjunctivitis (VKC) is a rare (1–10.6:10.000) (Kumar 2009) severe usually bilateral—although sometimes asymmetrical or unilateral—seasonal allergic inflammatory disease (Awwad *et al.* 2006). It is characterized by an inflammation of the ocular surface usually involving the upper tarsal and/or bulbar conjunctiva. VKC is two times more common in boys than girls. Onset is generally before age 10. The disease tends to regress around puberty (Abelson and Granet 2006; Kumar 2009; De Smedt *et al.* 2013). VKC can develop after puberty; in this case, there is a more equal gender distribution. The initial seasonal attacks in spring and summer may turn into perennial disease after a few years, being not just limited to spring, with episodes of reactivity being quite common in the winter (Kumar 2009).

Although it is a self-limiting disease, patients with VKC may demonstrate periodic exacerbation of inflammatory symptoms with a consequent decline of the quality of life and with a risk of permanent corneal damage that can be vision-threatening. Symptoms often tend to disappear 4–10 years after onset. It occurs more frequently in children who have a history of seasonal allergy, asthma, and eczema. In a study done by Zicari *et al.* (2013) 46% of VKC patients were found to have a family history positive for immune dysfunction.

Although its prevalence is higher especially in hot and dry climates (Mediterranean areas, Indian subcontinent, Central and West Africa and South America), and is more common in persons of Asian or African origin, VKC has a wide geographical distribution (Kumar 2009).

Vernal keratoconjunctivitis was first mentioned in the ophthalmic literature as conjunctiva lymphatica more than 150 years ago. Subsequently, most of the notables of ophthalmology during

that period (Arlt, Dasmarres, von Graefe, Axenfeld, Trantas, and Herbert) published about this interesting disorder. Different authors, at different times, described it as spring catarrh, phlyctenula pallida, circumcorneal hypertrophy, recurrent vegetative conjunctiva, verrucosa conjunctiva, and aestivale conjunctiva, calling attention to the various aspects of this disease (Kumar 2009).

Symptoms and Signs

Vernal keratoconjunctivitis is characterized by intense ocular itching exacerbated by exposure to wind, dust, bright light, hot weather, or sweating. Tearing, mucous discharge, conjunctival hyperemia, photophobia, blepharospasm, eye pain, foreign body sensation, and sometimes ptosis may be seen.

There are two forms of the disease: limbal or palpebral, depending on which portion of the conjunctiva is predominantly affected. Clinical examination may reveal a thin, copious milk-white fibrinous secretion (composed of epithelial cells, eosinophils and Charcot–Leyden crystals). *Palpebral involvement* may include conjunctival hyperemia and edema with papillae (filled with inflammatory cells) on the superior tarsal conjunctiva (Fig. 2). Giant papillae are seen as the disease progresses due to fibrous tissue proliferation and can reach 7–8 mm in diameter (so-called "cobblestone" papillae). Fibrin may accumulate on the giant papillae and is known as the Maxwell-Lyons sign. VKC patients can also show Dennie-Morgan line. Persistent forms of VKC are associated with subepithelial fibrosis that appears as a white linear scar running parallel to the lid margin (Arlt's line). *Limbal involvement* includes transient confluent gelatinous limbal papillae and clumps of necrotic eosinophils with dead epithelial cells and neutrophils on the limbus or conjunctiva seen as yellow-white points (Horner's points and Trantas dots) and conjunctival hyperemia with edema (Figs. 3 and 4) (Kumar 2009). Trantas dots tend to appear when VKC is active, and disappear when symptoms decrease (Friedlaender 2011), while the cobblestones persist even during quiescent phases of the disease. Corneal involvement is associated with more severe disease. Corneal epithelial punctate keratitis (called keratitis epithelialis vernalis of El Tobgy) may evolve to macroerosion, ulcers and plaques, which are all expressions of epithelial toxicity caused by factors released from activated eosinophils (Leonardi *et al.* 2008). The classic corneal change seen more commonly in patients with superior tarsal involvement, is the development of a non-infectious shield ulcer appearing as an irregular oval corneal plaque with elevated hypertrophic epithelial cells with fibrin and mucin that stains with fluorescein and contains eosinophils and epithelial cells (Fig. 5) (Udell *et al.* 1981; Abelson and Granet 2006). Superficial corneal neovascularization and sometimes filamentary keratitis may also occur (Zicari *et al.* 2013).

Although VKC is a bilateral disease, it may affect one eye more than the other.

Ocular complications of VKC include steroid-induced cataract, glaucoma and dry eye, corneal scarring, irregular astigmatism, microbial keratitis, limbal tissue hyperplasia, and keratoconus (Tabbara 1999; Sridhar *et al.* 2003). Amblyopia seen among VKC may be caused by corneal opacity, irregular astigmatism, and keratoconus (Kumar 2009). A common corneal degenerative change is pseudogerontoxon, in which there is increased lipid deposition in the peripheral portion of the cornea resembling corneal arcus senilis (Fig. 4).

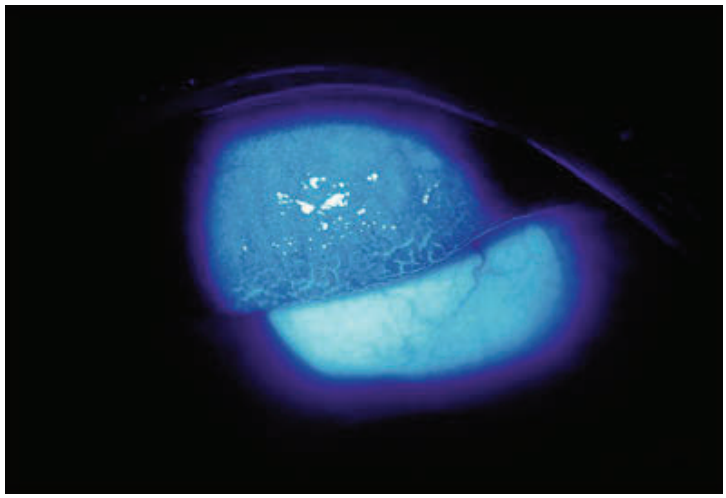

Fig. 2: Papillae in upper tarsal conjunctiva in vernal keratoconjunctivitis.

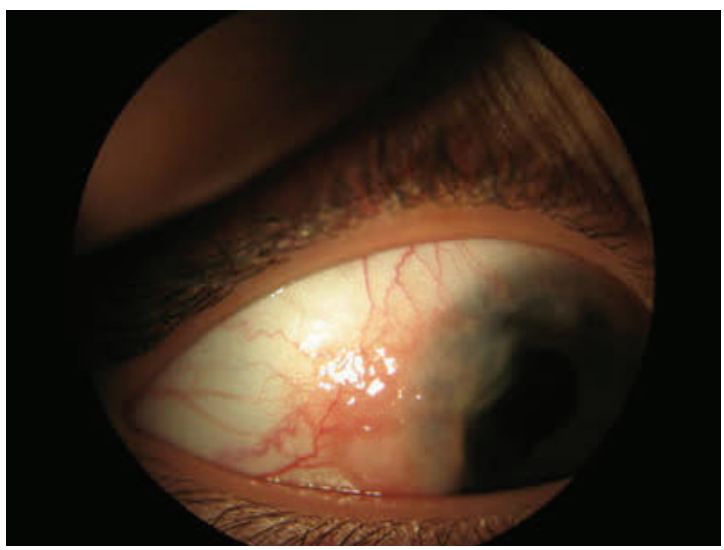

Fig. 3: Limbal involvement in vernal keratoconjunctivitis: limbal gelatinous hyperplasia with Horner–Trantas dots.

No precise diagnostic criteria have been established for this disease. Diagnosis is based on typical and characteristic clinical signs and symptoms; thus many mild or atypical cases may escape diagnosis. The diagnosis is based on the classical symptoms of allergic conjunctivitis (itching, tearing and hyperemia), and on specific ocular signs such as proliferative lesions in the conjunctiva including giant cobblestone papillae on the upper palpebral conjunctiva, limbal proliferation with limbal gelatinous hyperplasia and Horner–Trantas dots (Fig. 3) and the corneal findings described above. Even though atopy is common among VKC patients, only 50% of patients with VKC has positive skin prick test and/or elevated allergen-specific antibodies (Pucci *et al.* 2003; Bonini 2004). Increased total IgE antibodies in serum and lacrimal fluid eosinophils in the conjunctival smear are common findings.

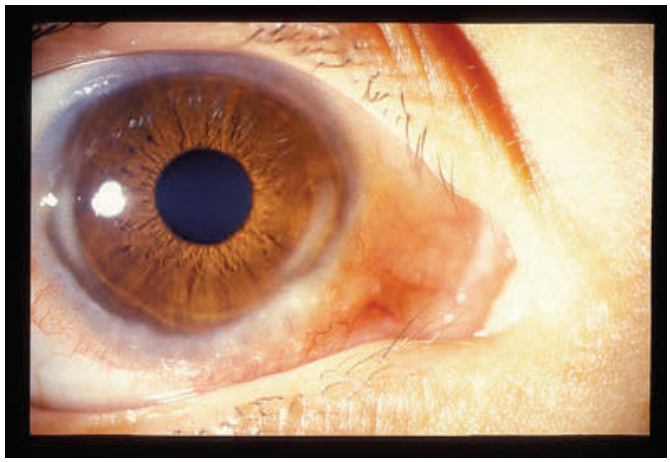

Fig. 4: Limbal involvement with limbal hyperplasia, pannus and pseudogerontoxon in vernal keratoconjunctivitis.

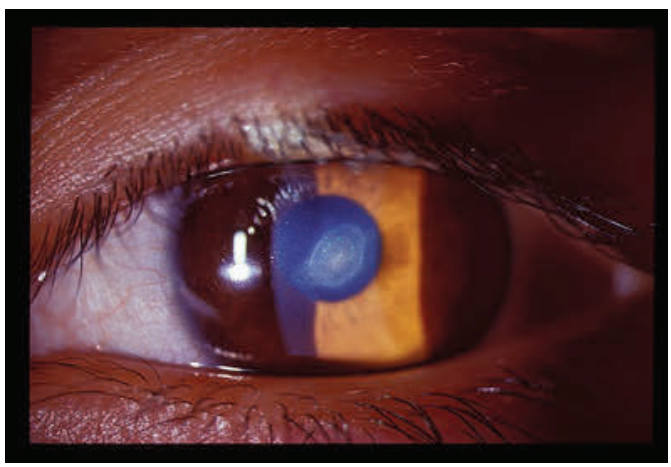

Fig. 5: Shield ulcer in vernal keratoconjunctivitis.

Pathogenesis

Ocular symptoms result from a nonspecific hyperreactivity induced by nonspecific stimuli, such as wind, dust, and sunlight, which is not related to allergen levels in the environment (La Rosa *et al.* 2013). Immunological data has proved that the pathogenesis of VKC is a type 1 and type 4 hypersensitivity reaction. Recently, many authors have suggested the existence of a cooperation between the allergic (Th2 mediated) and the inflammatory (Th1 mediated) responses (Leonardi *et al.* 2006; Zicari *et al.* 2013). The immunopathogenesis of VKC is multifactorial involving a Th2 mediated mechanism with an overexpression of Th2-derived cytokines, growth factors, mast cells, eosinophils, neutrophils, lymphocytes, and corneal fibroblasts that perpetuate the ocular allergic inflammation (Leonardi *et al.* 1999; Trocme and Sra 2002; Kumagai *et al.* 2006). In VKC, antigen presenting cells, such as Langerhans cells, are associated with co-stimulatory molecules (CD86)

that provide an important mechanism for Th2 cell activation (by interacting with CD28) and further cytokine release (Abu-El-Asrar *et al.* 2001a).

In the type 1 hypersensitivity reaction, ligands expressed in conjunctival B cells such as CD23, CD21, and CD40 are crucial for the interactions in the production of IgE (Abu-El-Asrar *et al.* 2001b). The tears of VKC patients contain high levels of IgE, histamine and mast cell mediators, including major basic protein (MBP), eosinophil cationic protein (ECP), Charcot–Leyden crystals, basophils, IgE- and IgG-specific for aeroallergens (e.g., ragweed pollen) and eosinophils (Ballow and Mendelson 1980; Irani *et al.* 1990; Bielory 2000). Chemokines such as IL-4 and IL-13 are involved in the formation of giant papillae by inducing the production of extracellular matrix and the proliferation of conjunctival fibroblasts (Leonardi *et al.* 2007). IL-8 in the extracellular space of the conjunctival epithelium plays an important role in the recruitment of neutrophils and eosinophils and in the pathogenesis of corneal damage in severe allergic diseases (Miyoshi *et al.* 2001). Degranulated eosinophils and their toxic enzymes such as ECP and MBP have been found in the tears and conjunctiva as well as in the periphery of corneal ulcers, suggesting their etiopathogenic role in many of the problems associated with VKC (Bielory 2000).

The increased conjunctival infiltration with eosinophils, basophils, mast cells, plasma cells, lymphocytes, macrophages, and fibroblasts, when compared to seasonal and perennial allergic conjunctivitis, may contribute to the serious complications seen in VKC (Trocme and Sra 2002). Granules with cytotoxic mediators are secreted by eosinophils releasing major basic protein, eosinophil cationic protein, eosinophil peroxidase, and gelatinase B which damage corneal epithelium and affect wound healing (Trocmé *et al.* 1993, 1997; Abu-El-Asrar *et al.* 2001c). Enzymatic degradation of histamine has been shown to be significantly lower in patients with VKC compared with normal patients in both tears and plasma, suggesting that this dysfunction may be a primary factor in the pathophysiology of VKC (Abelson *et al.* 1995).

Treatment of Allergic Eye Diseases

Treatment of pediatric ocular allergy should be managed by the ophthalmologist in conjunction with the allergist and in a multifactorial approach. Table 1 shows a summary of a suggested treatment approach. Avoidance of offending allergens as much as possible in conjunction to allergy medications is the mainstay therapy. For severe cases, topical corticosteroids and immunotherapy may be necessary. It is important to optimize the treatment of children suffering from allergic disease to improve their quality of life and avoid secondary complications.

Primary Interventions

Primary interventions, such as environmental modification and minimizing or avoiding the offending allergens as much as possible, are an important first step for all types of allergic conjunctivitis. For the more common allergens, simple measures including installing high-efficiency air filters and air conditioning, meticulous removal of dust such as vacuum cleaners with special filters, removal of drapes and carpets, protective goggles, sealing bedding, washing linens in hot

Table 1: Summary of suggested treatment approach.

Mild seasonal allergies
1. Avoidance of allergens and rubbing
2. Preservative-free artificial tears
3. Multimodal allergy medications over the counter, used as needed
Vernal keratoconjunctivitis (VKC) or atopic keratoconjunctivitis (AKC)
1. As above plus
2. Multimodal allergy medications used continuously
3. Cyclosporine 0.05% up to 4 times daily
4. Topical steroids for acute flares
5. Consider immunomodulatory shots
6. Control of dermatitis (AKC)
7. Control of systemic allergy (AKC and VKC)

water, avoidance of pets or keeping pets out of the sleeping areas and washing the child's hair in the evening prior to sleeping, can keep the allergen away from the eyes and the upper respiratory system. Some of these recommendations, especially involving beloved pets, can be difficult to implement. Cold compresses may aid in symptom relief, especially ocular pruritus. Eye lubricants, ideally preservative-free artificial tears, provide a barrier function and help to improve the first-line defense at the level of the conjunctival mucosa, helping to wash out or dilute allergens and inflammatory mediators of the ocular surface. Ointments are commonly used at night and provide moisture to the ocular surface while the child sleeps. Although frequently unsuccessful, discouraging of rubbing the itchy eyes is important.

Secondary Interventions

Topical pharmacological interventions may be required when non-pharmacological strategies do not provide adequate symptom relief. Milder cases can be treated with short-term topical ophthalmic therapy for temporary symptom relief such as decongestants, antihistamine with/without decongestants combination, mast cell stabilizers, a multiple action anti-allergic agent and anti-inflammatory agents.

Topical decongestants have shown to be effective, administered up to four times daily. These medications act as vasoconstrictors, effectively reducing ocular erythema, but have no effect on the allergic inflammatory response. Adverse effects include burning and stinging on instillation, mydriasis and rebound hyperemia with chronic use, and tachyphylaxis (Abelson *et al.* 1990). Their primary contraindication is in patients with narrow angle glaucoma. Phenylephrine and tetrahydrozoline are sympathomimetic agents that decrease congestion and edema through α-receptor stimulation.

Antihistamines competitively and reversibly block histamine receptors. Topical treatments are preferred over systemic for ocular allergies because of their greater efficacy in relieving itching and redness. However, systemic control of allergy is an important part of the management of

ocular allergy. These medications may need to be given up to 4 times per day, and may be irritating to the eye with prolonged use (La Rosa *et al.* 2013). Combined use of an antihistamine and a vasoconstricting agent is more effective than use of either agent alone. Moderate to severe cases may require longer usage of the above agents and the addition of an oral antihistamine. The combination of H1 receptor blockers with oral antihistamines provides a greater relief than oral antihistamines alone. Newer second-generation oral antihistamines (i.e., terfinadine or loratadine) may be preferred over first-generation antihistamines because they have reduced side effects such as somnolence; however they can induce ocular drying, and worsening allergic symptoms (La Rosa *et al.* 2013). In addition, ocular challenge testing has shown that use of systemic antihistamines can also result in a several-fold increase in allergen tolerance in both children and adults (Abelson and Granet 2006).

Mast cell stabilizers inhibit the degranulation of mast cells and thus suppress release of inflammatory mediators (e.g., histamine, leukotriene, thromboxane A2). These agents inhibit the early phase reaction of type I allergy and conjunctival local infiltration of inflammatory cells, both of which result in a reduction of the late phase reaction. Mast cell stabilizers do not relieve existing symptoms but they can be used on a prophylactic basis to decrease/prevent degranulation of mast cells, preventing release of histamine and other chemotactic factors. They require a loading period during which they must be applied before the antigen exposure. The exact mechanism of action is not known, but these agents may stabilize cell membranes through increased calcium influx or a reduction in membrane fluidity. Lodoxamide 0.1% has been used continuously for up to 3 months in children aged 2 years and older and pemirolast potassium 0.1% has been used to treat children 2 years and older without serious adverse effects (Abelson and Granet 2006).

Multimodal anti-allergic agents are the drugs of choice for providing immediate symptomatic relief. These multiple action drugs include olopatadine, ketotifen, azelastine, epinastine, and bepotastine, amongst others. They have multiple pharmacological effects such as histamine receptor antagonist action (H1, H2), stabilization of mast cell degranulation, and suppression of activation and infiltration of eosinophils, generation of leukotrienes and cytokine release. Olopatadine 0.1% is both a mast cell stabilizer and antihistamine with high affinity and selectivity for H1 receptors. In both adults and children as young as 4 years old, it has been shown to be superior to numerous anti-allergic agents (Abelson and Granet 2006). It is one of few agents approved by the US Food and Drug Administration (FDA) for treatment of all signs and symptoms of allergic conjunctivitis. Ketotifen 0.025%, a noncompetitive H1 antagonist and mast cell stabilizer, has proved safe and effective in the treatment of allergic conjunctivitis in children, although several studies have shown to cause mild stinging and shorter long-term duration of action than olopatadine (Abelson and Granet 2006). Azelastine 0.05%, a second-generation H1 receptor antagonist that inhibits histamine release from mast cells, downregulates ICAM-1 expression and prevents activation of inflammatory cells, has been shown to be safe in children aged 2 and older with allergic conjunctivitis (Abelson and Granet 2006).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally ineffective in chronic allergic conjunctivitis. Their therapeutic use is related to their ability to block prostaglandin biosynthesis by inhibiting the activity of cyclooxygenase. They can be used as additive drugs in order to reduce

hyperemia and pruritus related to prostaglandin D2 and E2, but they do not inhibit histamine (Saari 2010). An adjuvant course of aspirin, can be an effective strategy in treating severe cases of VKC (Abelson and Granet 2006).

Tertiary Interventions

If the previously mentioned approaches are not effective, immunomodulatory medications should be introduced.

Corticosteroids are one of the most potent agents used in the more severe variants of ocular allergy. Corticosteroids possess immunosuppressive and anti-proliferative properties, but their potential ocular adverse effects, such as delayed wound healing, secondary infection, elevated intraocular pressure, and cataracts must be taken into account. Newer topical steroids may have fewer side effects. Topical steroids are used for short courses in patients with inadequate response to secondary interventions and often tapered over several weeks after the acute flare while cell mast stabilizers are continued. Some children with severe disease may need longer courses of topical steroids. Corticosteroids require a loading period typically of 2 weeks before the maximum treatment effect is seen.

"*Steroid-sparing therapy*" calcineurin inhibitors such as cyclosporine or tacrolimus may be used as chronic therapy to reduce dependence on topical steroids.

Cyclosporine, a fungal antimetabolite used as immunomodulator, inhibits various inflammatory mediators and the development of mast cell-mediated allergic conjunctivitis. The use of topical cyclosporine 1% has shown to be effective to control symptoms and local inflammation in severe forms of VKC in childhood when applied at the beginning of the disease and for a long-time period (Tesse *et al.* 2010). Because cyclosporin A is lipophilic, it must be dissolved in an alcohol–oil base, which may cause ocular irritation (i.e., burning, tearing, erythema, and itching).

Tacrolimus is a macrolide antibiotic that has potent immunomodulatory properties. Tacrolimus acts primarily on T lymphocytes by inhibiting the production of lymphokines, particularly IL-2, as well as IL-3, IL-5, TNF-α, and IFN-γ. Tacrolimus blocks degranulation of mast cells as well as activation of their cytokines. This drug is highly efficient to prevent post-transplant rejection in patients resistant to steroids and cyclosporine. In this regard, tacrolimus is between 10 and 100 times more powerful than the latter (Hooks 1994). It has been effective in the treatment of a variety of other ocular immune-mediated diseases such as corneal graft rejection, keratitis, scleritis, ocular pemphigoid, and uveitis (Bielory 2000). Regarding the current limited data from literature, ocular application of tacrolimus 0.1%, 0.03% and 0.02% seems effective in treating patients with allergic keratoconjunctivitis; however, ocular irritation may limit its use. Because of the risk of development of herpes keratitis, adequate follow-up is advised (Sánchez Ferreiro and Muñoz Bellido 2013; Westland *et al.* 2013). At present, tacrolimus cream is available in two approved concentrations (0.1 and 0.3%) by the FDA for skin use in the treatment of atopic dermatitis, but topical ophthalmic drops must be compounded.

Immunotherapy, whether via the subcutaneous route or the intranasal or sublingual route, should be considered in the treatment of persistent severe cases refractory to conventional

treatment. Allergen-specific immunotherapy is an effective treatment for patients with allergic rhinoconjunctivitis who have specific IgE antibodies to allergens inducing clinical tolerance to the specific antigen. However, the immune responses to allergen administration are not predictive of the effectiveness of the therapy and the therapy itself can produce systemic reactions depending on the type of allergen administered (La Rosa *et al.* 2013). The sublingual (oral) immunotherapy is gaining momentum among allergists and it has been shown to control ocular signs and symptoms although less well than nasal symptoms, thus it requires further evaluation for the ocular allergy relief (La Rosa *et al.* 2011).

Systemic immune suppression is indicated for severe cases of ocular allergy unresponsive to topical treatment where progressive cicatrization is vision-threatening; this therapy should be managed in conjunction with a pediatric rheumatologist.

In the future, newer, more selective drugs like anti-chemokine receptor antibodies, leukotriene receptor antagonists, liposomal delivery systems, anti-IgE therapy and plasmid DNA immunization may become available for treatment of ocular allergy (Abelson and Granet 2006).

Conclusion

Ocular allergy has a wide spectrum of presentation. SAC and PAC, characterized by type 1 hypersensitivity reaction, are the least severe and easier to manage. VKC and AKC are more serious allergic disorders, characterized by types 1 and 4 hypersensitivity reactions with massive involvement of T cells, macrophages, and eosinophils which may cause severe complications. It is an important ocular disease due to potential sight threatening complications. Thus, it is critical to manage these patients in a multifactorial fashion in conjunction with the pediatrician, allergist, and ophthalmologist. The main objective is to be able to get these children through the disease successfully preventing the complications and possible iatrogenia.

Compliance with Ethical Requirements Kathryn Colby and Andrea Cruzat declare that they have no conflict of interest. No human studies or animal studies were carried out by the authors for this article.

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3

Allergic Rhinoconjunctivitis

Leonard Bielory, Preeti Wagle

Case Presentation 1

A 35-year-old male patient was referred to the allergist with persistent asthma, atopic dermatitis, rhinitis, and chronic conjunctivitis. The patient complains of symptoms related to eyes that include soreness and excessive tearing, which have been getting progressively worse over the last 10 years: yellowish mucoid discharge upon wakening for the last 5 years and photophobia for the last 9 months. In addition, for the past 6 months, he has had increased ocular discomfort, has started to squint constantly, and has had mild blurring of vision and worsening sensitivity to light without pain. He has been treated for these symptoms by many ophthalmologists over the years and has been prescribed various eye drops and oral medications. The patient's ophthalmologist noted increased curvature of the left cornea with mild keratitis.

His allergic rhinitis has been treated for the past several years with an intranasal corticosteroid. He chronically uses oral over-the-counter second-generation H1-antihistamines to control his sneezing.

The patient's asthma has been well controlled with an inhaled corticosteroid/long-acting beta-agonist therapy. He has had multiple courses of oral corticosteroids, but was never admitted to the hospital.

His atopic dermatitis is being treated with topically applied tacrolimus cream, and his symptoms of itching, redness, and scaling are under control.

His current medications include systemic prednisone (60 mg daily), topically applied (skin) tacrolimus cream, and triamcinolone. He also uses Lotemax™ (loteprednol), Alrex™ (loteprednol), and Vigamox™ (moxifloxacin) eye drops in the right eye four times daily; Restasis™ (cyclosporine) in the left eye twice daily; and Celluvisc™ (carboxymethylcellulose) in both eyes as needed.

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His family history is significant for his father having had a myocardial infarction and colorectal cancer and his mother having ovarian cancer.

The patient works as an administrator of an international accounting firm. His job requires extensive use of computer work in excess of 10 h per day. He was stationed in the Middle East for the past 7 years and just relocated to the United States. While in the Middle East he experienced seasonal exacerbations of chronic red eyes, tearing, droopy upper eyelids at times with a glassy appearance, as well as nasal congestion and a runny nose that never completely resolved.

The patient is a nonsmoker and occasionally drinks alcohol. He has also been a contact lens wearer for the last 20 years.

He is allergic to Dovonex™ (calcipotriol), a synthetic derivative of vitamin D cream, and has a history of intolerance to systemic cyclosporine (hypertension and nephropathy).

On physical examination, there is redness and swelling present around both eyes and cheeks, with increased creases below his eyes and a peculiar absence of the lateral eyebrows with eyelids that are slightly asymmetrical. There is thickening of both lids with redness, fissuring, and swelling. There are diffuse fine areas of pinhead-shaped and -sized lesions of the upper and lower tarsal conjunctiva, diffuse multiple blood vessels and increased thickness of the clear portions of the conjunctiva, and a white stringy semisolid thread of white mucus in the inferior fornix. The upper right eyelid touches the iris, with the left upper eyelid touching the pupil.

Discussion

The patient has extensive atopic conditions affecting the nose, skin, and lungs that are commonly treated by the allergists. However, with the assistance of the ophthalmologists it is apparent that the patient also has ocular involvement of his atopic condition, consistent with the diagnosis of atopic keratoconjunctivitis (AKC) with keratoconus.

Atopic keratoconjunctivitis (AKC) is a chronic allergic ocular disease that occurs most often in patients with a history of atopic dermatitis. The exact prevalence is unknown, but appears to be present to some degree in 5% of the atopic dermatitis patients. Thus, AKC is a relatively common disorder with varying degrees of severity. Its severity can be highly asymmetric even though the involvement in this case is bilateral. The periocular skin demonstrated scaling of the upper and lower eyelids with induration of the lower eyelid from the chronic allergic response and the topical application of a preservative-based ophthalmic medication resulting in chronic blepharoconjunctivitis.

Ocular allergy (OA) or allergic conjunctivitis (AC) is a term that refers to a collection of disorders that affect the eyelid and conjunctiva. The IgE-mast cell and non-IgE-mediated hypersensitivity disorders include seasonal and perennial allergic conjunctivitis (SAC and PAC), vernal and atopic keratoconjunctivitis (VKC and AKC), and blepharoconjunctivitis (contact and other variants) [1]. The use of in vivo and in vitro tests assists in identifying the specific allergic trigger(s). Although clinical characteristics support the diagnosis of OA, errors in the final diagnosis are not uncommon due to changing features of the initial or chronic presentations and the overlap with

pseudo-allergic forms that present with clinical manifestations similar to allergy but with a nonallergic equivocal pathogenesis. Ocular allergy is easily mimicked and often overlaps other anterior ocular surface disorders including tear film dysfunction, blepharitis, infections, and toxic and mechanical forms of conjunctivitis.

Keratoconus is a disease in which the shape of the cornea is progressively distorted. The cornea becomes thin and steep and protrudes anteriorly. The nature of the protrusion may be complete (oval or globus keratoconus) or localized to the center of the cornea (nipple cone). This results in progressive myopia, astigmatism, and increasing requirement for myopic spectacle prescriptions as the condition progresses. There is also intolerance to wearing contact lens as they sometimes fall off or get dislodged.

Management

The treatment choices for AKC include:

1. High-dose systemic corticosteroid therapy
2. Systemic tacrolimus 4 mg/day
3. Intravenous Zenapax (daclizumab), 75 mg/infusion (determined by his weight)

In the past, management of acute and more chronic forms of ocular allergy has focused on symptomatic relief, but with a better understanding of the mechanisms involved therapeutic strategies are now more focused [2].

The treatment of severe AKC involving the cornea should include involvement of an allergist working in conjunction with an ophthalmologist.

The identification of the allergenic triggers and education about avoidance of triggers are important aspects in the management of atopic disorders. The triggering antigen may be identified in patients by skin or serum-specific IgE testing against a panel of commonly occurring seasonal and perennial allergens.

Tacrolimus is an immunosuppressive drug (calcineurin inhibitor) used after organ transplants to prevent rejection. Severe AKC may be refractory to topical treatment and in these patients low-dose systemic tacrolimus may be used. However, the patient will need to be monitored for side effects such as infection, hypertension, and nephrotoxicity. In addition to systemic tacrolimus, tacrolimus ointment may be used to treat eyelid eczema in AKC patients [3].

Daclizumab is an immunosuppressive, humanized IgG monoclonal antibody produced by recombinant DNA technology that binds specifically to the alpha subunit (~55 alpha, CD25, or Tat subunit) of the human high-affinity interleukin-2 (IL-2) receptor that is expressed on the surface of activated lymphocytes. Daclizumab, approved for relapsing multiple sclerosis and administered 150 mg subcutaneously monthly, has shown to be effective for AKC in reducing concomitant immunosuppressive medications, stabilizing visual acuity, and preventing uveitic flares [4].

The patient's current medications include prednisone, the side effects of which include posterior subcapsular cataracts. Because one of the associated causes of ocular morbidity in patients

with AKC is a high incidence of cataracts (mostly anterior or posterior subcapsular), the patient should be monitored for this complication [5].

Case Presentation 2

The patient is a 27-year-old female who has been referred to the allergist for nasal and ocular complaints of tearing, redness and burning sensation, rhinorrhea, and nasal congestion. She complained of redness and burning of both eyes for the past 6 months that has progressed to increased bilateral tearing for the last month. When further questioned she also admitted to bilateral foreign body sensation and itching. She says that her ocular symptoms seem to increase as the day progresses. She stated that nasal congestion and sneezing developed in a seasonal pattern several years ago, for which oral antihistamines had been used with decreasing impact. She has maintained their use, but was also instructed to use an intranasal corticosteroid over the past year. She was told that it would help both her nasal complaints (especially nasal congestion) and eye symptoms. The patient has had skin prick testing performed 5 years ago after moving from Colorado to New Jersey that was positive for grass and tree pollens, dust mite, and cat allergens.

Her past medical history was remarkable for a laparoscopic appendectomy 8 years ago. Her current medications include cetirizine 10 mg daily and diphenhydramine 25 mg as needed which usually amounts to 2–3 times a week, at night, during the spring and summer. She is also taking Yaz, a combined oral contraceptive pill, daily for the last 4 years.

Her family history is significant for multiple pollen allergies in her mother and sister, whose symptoms are greatest between May and June as well as diabetes and hypertension in her father.

The patient is a nonsmoker and doesn't drink alcohol. She is married for 2 years and her husband smokes one pack of cigarettes daily indoors at home and while in the car. The patient works as a flight attendant; she used to fly on a domestic airline, but has recently switched to flying from New York to London. She notes that her ocular symptoms have worsened since working on longer flights. The patient previously lived in Denver, but moved to northern New Jersey 6 years ago. The patient was not diagnosed as being allergic to grass pollen until she moved to New Jersey. She has been wearing contact lenses 4–5 times a week for the past 13 years.

The patient has a history of a penicillin allergy since the age of 4 during which time she was treated with oral amoxicillin for acute otitis media and subsequently developed "hives" and pruritus within several hours of taking the first dose. Subsequently, skin testing to penicillin was performed by an allergist, which was positive.

Physical examination revealed redness and a stringy discharge in both eyes. There was mild inflammation of the lids bilaterally. Schirmer's test showed 9 mm of moisture after 5 min in both eyes. Fluorescein stained the cornea in numerous punctate regions. The nasal mucosa was bluish grey in color without evidence of swelling. Mild discharge was seen which was clear and watery. Palpation of the paranasal sinuses produced no pain. The oral mucosa was moist and otherwise unremarkable.

Discussion

A diagnosis of dry eye syndrome was made based on both the patient's symptoms of burning, itching, and foreign-body sensation and the physical exam which showed discharge, an abnormal Schirmer's test, and staining of the cornea with fluorescein.

Dry eye syndrome (DES) is a syndrome in which there is a decreased or absent production of tear film. Patients suffer from symptoms such as dryness, itching, redness, and a burning sensation of the eyes.

There is a significant overlap of symptoms between dry eye syndrome and seasonal allergic conjunctivitis. In patients with significant itchiness, there is a high probability that they also have dryness and redness, and the converse is also true. As seen in this patient, it is more common to start with allergic conjunctivitis (AC) and subsequently develop DES which can be exacerbated by the use of oral antihistamines [6]. Dry eye syndrome is also seen as part of the development of chronic forms of anterior surface disorders including ocular allergies [7].

The patient is currently taking both cetirizine and diphenhydramine, both of which are antihistamines, the first line of treatment in allergic rhinoconjunctivitis. However, studies have shown that these drugs also create problems with excessive drying, including the eyes. It appears that all antihistaminic drugs can cause abnormalities in tear film composition with the older formulations (e.g., first-generation H1-antagonists) having the greater anticholinergic activity [8].

Hormonal changes are also associated with various forms of ocular surface disorders. Oral contraceptives especially in those patients wearing contact lenses have been shown to be twice as likely to develop symptoms of dry eye as those patients who were not taking oral contraceptives [9].

Several environmental factors that are known to aggravate anterior surface disorders include cigarette smoke in her home [10], chronic use of extended-wear contact lenses, and occupational issues such as working as a flight attendant due to excessive dry airplane cabin air [11].

Management

Treatment choices for this patient include eye lubricants, lifitegrast, and cyclosporine. The treatment of DES begins with eye lubricants. Guar-based lubricants improve tear film stability. These formulas contain substances such as propylene glycol, hydroxypropyl guar borate, and sorbitol, as well as mineral oil and a phospholipid surfactant, that create an artificial lipid layer over the aqueous component of the tear film [12].

Lifitegrast, marketed as Xiidra™, is another drug being used for treatment of dry eye. It is an antagonist of lymphocyte function-associated antigen-1 that binds to intracellular adhesion molecule 1 (ICAM-1), which is overexpressed in dry eye, thereby potently inhibiting T-cell activation, adhesion, migration, proliferation, and cytokine release. It has been shown in trials to improve dryness and ocular discomfort. However, there was no difference in clinical findings such as light sensitivity and foreign-body sensation or tear breakup time. There was also no statistical difference in the Schirmer's test. Adverse effects include eye irritation and blurred vision [7, 13].

Table 1: Differential diagnosis of ocular allergy.

	AKC	VKC	SAC	PAC	GPC	CBC	VC	BC	Dry Eye	Sjögren's Syndrome	KCS
Conjunctival redness											
Photophobia											
Conjunctival giant papillae											
Limbal inflammation											
Chemosis											
Mucoid discharge											
Watery discharge/ Tearing											
Lid eczema											
Itching											
Burning			-	-							
Blepharitis											
Conjunctival papillae											
Conjunctival follicles											
Superficial punctate keratopathy, corneal scars, pannus											
Corneal shield ulcer or plaque											
Pain											
Nasal Symptoms											
Dry oral mucosa											
Foreign body sensation											

Symptoms present
Symptoms especially present
Symptoms may or may not be present
Symptoms are severe

Abbreviations: *AKC* atopic keratoconjunctivitis, *VKC* vernal keratoconjunctivitis, *SAC* seasonal allergic conjunctivitis, *PAC* perennial allergic conjunctivitis, *GPC* giant papillary conjunctivitis, *CBC* contact blepharoconjunctivitis, *VC* viral conjunctivitis, *BC* bacterial conjunctivitis, *KCS* keratoconjunctivitis sicca

Restasis™, or cyclosporine, has been long recognized for its use in dry eye syndrome. It is an inhibitor of T-cell activation and has been shown to decrease activated T-cells. It also prevents the release of various cytokines. Cyclosporine emulsion has been shown in studies to increase goblet cell density and production of the immunoregulatory factor TGF-beta 2 in the bulbar conjunctiva [14].

Table 1 shows the signs and symptoms to be used in the differential diagnosis of ocular allergy. Conjunctival redness is seen with various intensities in all types of anterior surface disorders. Clinical features such as mucoid discharge, conjunctival giant papillae, limbal inflammation, lid eczema, superficial punctate keratopathy, corneal scars, pannus, corneal shield ulcer or plaque, and pain can assist in further differentiating more chronic forms of ocular allergy (e.g., AKC and VKC) versus milder acute forms such as SAC and PAC. When making a diagnosis between AKC and VKC, blepharitis and burning are more commonly seen in AKC than VKC.

Dry eye syndrome can be differentiated from Sjögren's syndrome and keratoconjunctivitis sicca by the severity of symptoms. Patients with non-Sjögren's aqueous tear deficiency do not have symptoms as severe as those with Sjögren's syndrome [15]. Watery discharge is seen in some forms of dry eye syndrome due to increased reflex tearing, but in Sjögren's syndrome and keratoconjunctivitis sicca associated with fibrosis of the lacrimal glands severe dryness ensues. Itching is seen in dry eye syndromes, but not seen in Sjögren's or keratoconjunctivitis sicca. Dry eye syndrome also needs to be differentiated from allergic conjunctivitis as there is significant overlap between the two conditions. Although conjunctival redness, itching, foreign-body sensation, and discharge are seen in both conditions, chemosis is not commonly seen in dry eye syndrome, but is seen in allergic conjunctivitis. Nasal symptoms are seen in 90% of patients with allergic conjunctivitis and not in DES.

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4

Diagnosis and Management of Conjunctivitis in Infancy and Childhood

Alison E. Smith, Michelle M. Ariss

Abstract

The evaluation of the child with a red eye can be challenging, as the differential diagnosis is broad and the performance of an adequate exam in this age group can sometimes be difficult. Following a paradigm and looking for specific signs and symptoms and historical clues, combined with careful examination facilitates the identification of the underlying etiology.

Keywords: Conjunctivitis, Red eye, Atopic conjunctivitis, Vernal conjunctivitis, Ophthalmia neonatorum

Introduction

Conjunctivitis is one of the most common ocular infections in childhood and accounts for up to 15 % of ophthalmologic and 6 % of primary care physician consultations [1]. A thorough understanding of this group of conditions is necessary to provide optimal eye care to children [2].

The major categories of childhood conjunctivitis are infectious and noninfectious. The two main categories of infectious conjunctivitis are viral and bacterial. Bacteria cause up to 70–80 % of cases in children [3]. Viral cases, most commonly due to adenovirus, vary depending on the serotype. Some serotypes are responsible for epidemic keratoconjunctivitis (EKC) (types 8, 19, and 37), while others cause pharyngoconjunctival fever (types 3 and 7), acute hemorrhagic

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conjunctivitis (types 11 and 21), or acute follicular conjunctivitis (types 1–4, 7, and 10). Both bacterial and viral conjunctivitis are highly contagious and appropriate isolation should be addressed and discussed with family members in order to help limit spread.

Neonatal conjunctivitis is contracted during passage through the birth canal, or as a result of the infectious agent ascending to the uterus and infecting infants born via cesarean. Neonatal conjunctivitis carries the risk of systemic spread and the possibility of associated meningitis or pneumonitis hence its management may entail hospitalization and systemic treatment.

Noninfectious etiologies of childhood conjunctivitis include atopic keratoconjunctivitis and vernal keratoconjunctivitis.

The characteristics of each of these major groups, including signs, symptoms, and optimal management, are discussed in the following sections, with the purpose of helping to identify the cause and to plan appropriate management of children with acute conjunctivitis.

Bacterial Conjunctivitis

Bacterial conjunctivitis, characterized by mucopurulent discharge and conjunctival injection, is contracted through direct contact with secretions and/or contaminated objects.

The associated discharge is copious and thick, often green-tinged or yellow-white in color. The discharge is present in the conjunctival cul-de-sac with crusting or matting of the lashes.

The most common pathogens are *Streptococcus pneumonia*, *Haemophilus influenza*, and *Moraxella catarrhalis* and account for roughly 55–68 % of cases in children [4]. The incidence of *Haemophilus* infections has dropped with widespread use of immunizations. Cultures are not necessary before the initiation of treatment, and may yield false positive results. An exception is made for the patient suspected to be infected with *Neisseria* in whom a Gram stain and culture should be obtained as *Neisseria gonorrheae* is vision-threatening with high risk of progression to corneal perforation, and *N. meningitidis* may spread systemically and cause meningitis [1]. A hyperpurulent discharge is characteristic of gonococcal conjunctivitis.

While many cases of conjunctivitis are self-limited, the use of topical antibiotics can shorten the course of infection. A study by Gigliotti *et al.* [5] found that the bacterial pathogen was eradicated at days 3–5 in 70 % patients treated with a topical antibiotics, compared to only 19 % in the placebo group.

A Cochrane Review of studies comparing placebo versus antibiotics for acute bacterial conjunctivitis concluded that although frequently self-limiting, antibiotics did hasten the recovery from infection and the resolution of symptoms in patients with acute bacterial conjunctivitis, thereby supporting their use in the treatment of acute bacterial conjunctivitis. Various studies have been conducted to identify ideal topical antibiotic agents for the treatment of bacterial conjunctivitis in children. Polymyxin and bacitracin ointment used four times per day is effective in clinically proven cases of *H. influenza* and *S. pneumonia* in patients between the ages of 1 month and 18 years [4]. Increasing antibiotic resistance has resulted in more widespread use of the fluoroquinolones. But when studied by Gigliotti and Williams, fluoroquinolones (specifically moxifloxacin) were not found to be superior to polymyxin B-trimethoprim in the treatment of acute

conjunctivitis by day 7–10 of treatment, suggesting that polymyxin B-trimethoprim can be safely used as a first line agent [4].

Although azithromycin was shown to be superior to tobramycin in resolving clinical symptoms at day three of treatment, they were both shown to be equally effective at curing conjunctivitis associated with purulent discharge by day 7 [6]. In cases of *Neisseria* and *Chlamydia*, management should include the systemic administration of antibiotics because of the risks of meningitis and pneumonitis, respectively.

Systemic treatment will be discussed in more detail in the section regarding management of neonatal conjunctivitis.

Hence it appears that adequate first line agents include erythromycin or polytrim [7]. If there is no improvement of signs and symptoms after a few days, other agents with broader coverage including bacitracin, fluoroquinolones, or azithromycin can be used. Aminoglycoside drops carry a risk of corneal toxicity and may not be the best first choice [8]. Fluoroquinolones should not be used first because of concerns over emerging resistance. One exception is the contact lens wearer with signs of conjunctivitis. These patients should stop all contact lens wear and discard potentially infected contact lenses. Contact lens wear can be resumed once the infection has subsided and a course of topical antibiotic therapy has been completed.

Viral Conjunctivitis

Case 1 Clinical synopsis: A 5-year-old girl presents to the ophthalmologist's office with a one-day history of red burning right eye. Visual acuity was 20/40 OD and 20/20 OS. Her mother reported that the entire family has had upper respiratory tract infections over the past few weeks. Slit lamp examination of the right eye revealed 4–5 subepithelial infiltrates of the cornea as well as 2+ conjunctival injection. The anterior chamber was quiet. There was no purulent discharge. She was treated for presumed viral conjunctivitis and a suspicion for EKC, with education about effective hand washing and frequent artificial tear use. Because of decreased vision and corneal involvement she received prednisolone acetate 1 % drops four times/day for 5 days. Upon her follow-up visit her vision was back to 20/20 in the affected eye and her ocular discomfort as well as corneal changes had resolved. The steroids were stopped and the patient was educated to follow-up as needed.

Comment Unlike the purulent white discharge of its bacterial counterpart, viral conjunctivitis presents with unilateral or bilateral watery serous discharge from a hyperemic eye. A follicular conjunctival reaction is usually present and can be visualized on slit lamp examination. Eye findings may be isolated or combined with a viral prodrome consisting of lymphadenopathy, fever, pharyngitis, or upper respiratory tract infection. Viral conjunctivitis is highly contagious and, like bacterial conjunctivitis, spreads through direct contact with infected patients, or contaminated surfaces. The most common pathogen identified in viral conjunctivitis is the DNA virus, adenovirus. To date, 68 serotypes of adenovirus have been reported (Human Adenovirus Working Group http://hadvwg.gmu.edu/). Various serotypes account for conjunctivitis as well as other systemic diseases such as gastroenteritis, hepatitis, myocarditis, and pneumonia.

Epidemic Keratoconjunctivitis (EKC)

A highly contagious type of viral conjunctivitis caused by adenovirus is EKC. Adenoviral serotypes 3, 4, 8, 19, and 37 are associated with EKC. Of these, serotypes 8, 19, and 37 have been reported to cause the most severe conjunctivitis [9]. EKC is associated with systemic symptoms of fever, malaise, respiratory complaints, myalgia, as well as ocular symptoms of redness, photophobia, foreign body sensation, and tearing. Ipsilateral preauricular lymphadenopathy is a common finding with EKC. Associated eyelid swelling and conjunctival hemorrhage may also be present.

Differentiating EKC from other forms of conjunctivitis is the presence of associated corneal abnormalities, which can prompt complaints of blurred or decreased vision. Punctate keratopathy often occurs within a few days of onset of symptoms and can coalesce into focal epithelial keratitis that can persist for roughly 2 weeks or more [10]. Within the subepithelial layer beneath the focal lesions, infiltrates may develop which can leave scars that persist for months to years [11]. These subepithelial infiltrates are the result of an immune response to adenoviral antigens within the corneal stroma.

With the use of confocal microscopy, corneal structural changes have been identified during the course of infection [10]. As reported by Dosso and Rungger-Brandle [10], follicular conjunctivitis and focal keratitis occur within 1 week of symptoms, associated with clusters of dendritic cells and keratocytes in the anterior stroma. Subepithelial infiltrates occur by week 2. A higher number of infiltrates are associated with a decrease in visual acuity. By week 4 of infection, patients are usually asymptomatic, however, confocal microscopy reveals persistence of dendritic cells and keratocytes. By 24 weeks after the onset of symptoms, when epithelial and anterior stromal dendritic clusters have resolved, high reflectivity may persist in the mid stroma, suggesting late stromal wound healing in EKC.

Because of the absence of effective antiviral therapy and the spontaneous recovery in most cases, management of EKC is predominantly supportive with artificial tears and cool compresses, and complete resolution occurs within 3 weeks in most cases [12]. The use of topical steroids should be reserved for more complicated cases associated with pseudomembranes or extensive subepithelial infiltrates and reduced vision; animal models have suggested an increase in replication of the virus as well as duration of infection, most notable in the later phase of infection (days 9–21) if steroids are used continuously for up to 18 days. The alteration of adenoviral replication has been shown with both higher potency steroids such as prednisolone acetate 1 % and low potency steroids such as prednisolone acetate 0.12 % [13]. Topical cyclosporine A has been shown to reduce subepithelial infiltrates, yet promote viral shedding and prolong the duration of infection [14], thereby increasing the risk of spread and of epidemics. Topical NSAIDs appear to have no effect on adenoviral clearance, but can provide relief of symptoms [15].

A rapid test for the detection of the adenovirus in acute conjunctivitis is available and may be helpful in confirming a clinical diagnosis, hence assisting in treatment and patient education [16]. Due to the highly contagious nature of EKC, patients suspected of having this condition should be kept out of school for 1–2 weeks until signs and symptoms have subsided.

Pharyngoconjunctival Fever

Pharyngoconjunctival fever is a specific clinical presentation of adenovirus infection. Typically it manifests with a high fever lasting an average of 4–5 days with pharyngitis, conjunctivitis, regional lymphoid hyperplasia, and other symptoms associated with viral prodrome. It is very common in the pediatric age group. Transmission occurs through contact with infected upper respiratory droplets or fomites, or through swimming pools, in which fecal contamination containing the virus is believed to be responsible. The incubation period averages 8 days. Management follows the same protocol as those previously mentioned for viral conjunctivitis [17].

Allergic Conjunctivitis

Case 2 Clinical synopsis: An 8-year-old boy presents with a 1-month history of chronic red eyes associated with itching. His mother does not report recent upper respiratory tract infections but comments that her son has eczema and seasonal allergies. The key exam features include: normal vision, Horner-Trantas dots, conjunctival papillae and injection in both eyes. The patient was diagnosed with vernal keratoconjunctivitis and effectively treated with initiation of a mast cell stabilizer, one drop daily (olopatadine hydrochloride 0.2 %) and a very short course of steroids (fluorometholone 1 %, 4 times daily for 5 days). There was marked improvement of signs and symptoms within a few days of the initiation of treatment.

Comment Allergic conjunctivitis encompasses more than one condition with the hallmark symptoms of itching and eye rubbing. Under the umbrella of allergic conjunctivitis are the conditions of seasonal allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. The following section will elaborate specifically on vernal and atopic conjunctivitis.

Vernal Keratoconjunctivitis

Vernal conjunctivitis is a severe form of ocular surface allergy that, if left untreated, can cause permanent visual deficits through scarring of the corneal surface. The word vernal literally means "related to or occurring in the spring." This condition most often affects individuals who live in warm climates and is more prevalent in warm weather months. It is associated with other atopic manifestations such as allergic rhinitis, asthma, or eczema, in approximately one-half of patients. Males are more often affected than females. As with seasonal allergies, many children outgrow the disease as they approach puberty. Vernal keratoconjunctivitis is associated with high tissue levels of IgE and various inflammatory mediators, hence, responds well to mast cell stabilizers.

Symptoms generally include itching with associated eye rubbing, often with redness, eyelid swelling, and mucus discharge. Additional symptoms can include pain, burning, and, if the cornea is involved, photophobia. On slit lamp examination, a papillary reaction can be seen on the conjunctiva. Almost all children have large papillae on the upper tarsal conjunctiva. These giant papillae are the result of IL-4 and IL-13 mediated proliferation of conjunctival fibroblasts, and filled with inflammatory cells and edema.

Other signs include Horner-Trantas dots (eosinophil aggregates), corneal shield ulcers, and blepharospasm. Horner-Trantas dots form as eosinophils collect in crypts at the limbus. They often appear during active VKC and resolve when symptoms subside.

Shield ulcers often occur in the superior cornea, and appear as oval-shaped epithelial ulcers with underlying stromal opacification. They are sterile in nature. Other sight-threatening corneal findings in VKC include neovascularization and scarring. In contrast to vernal keratoconjunctivitis, atopic keratoconjunctivitis nearly always presents with corneal scars and neovascularization and predominately affects the lower lids.

To manage this immune-mediated condition, initial treatment requires the use of mast cell stabilizers and antihistamines. Olopatadine is an anti-allergy agent with selective H1 antihistaminic and mast cell stabilizing properties that works well as a first line dual-mechanism agent therapy [18]. Other agents with these two properties include ketotifen fumarate (Alaway), azelastine (Optivar), pemirolast potassium (Alamast), and epinastine (Elestat). If there is corneal involvement on presentation or limited response to the aforementioned drugs, corticosteroid drops may be indicated. Depending on the severity of the disease, the physician may choose prednisolone acetate 1 % (Pred Forte®), fluorometholone 0.1 % (FML Forte®; FML Liquifilm®), loteprednol % (Lotemax®), or rimexolone 1 % (Vexol®). Steroids are frequently given as a high dose short course of 1 drop 4–8 times daily for 1 week, then quickly taper. The use of steroids should be closely monitored for side effects such as glaucoma or cataract formation. Severe cases may also require oral therapy or referral to an allergist for systemic immunomodulation.

Refractory cases or ones associated with corneal epithelial defects may benefit from topical treatment with calcineurin inhibitors. Their use may provide long-term benefits by avoiding side effects associated with chronic steroid use. The two most commonly used medications are tacrolimus (Protopic®) and cyclosporine (Restasis®). Ophthalmic cyclosporine has been tested and shown to be effective in treating patients with VKC. Utilization of the drug showed a statistically significant decrease in the signs and symptoms over a 6-week period [19]. An Italian study found similar results and determined that most of the therapeutic effect occurs quickly, within 2 weeks [20].

Although typically sterile, corneal shield ulcers should be treated similarly to other corneal ulcers with culture and coverage with broad-spectrum antibiotics until culture results are obtained.

It is important to educate patients to limit eye rubbing and to use cool compresses for symptomatic relief of itching.

Atopic Keratoconjunctivitis

Atopic conjunctivitis (AKC) is a chronic bilateral allergic ocular disease that is perennial and typically affects older individuals. Most patients have additional atopic manifestations such as dermatitis or eczema. Thus, eczematous skin lesions may be seen on the eyelids as well. Blepharitis and scurf are commonly found on the lashes and patients may have staphylococcal superinfections. In contrast to VKC the lower eyelid is often involved and can appear swollen. Cicatricial entropion may develop secondary to chronic inflammation and conjunctival scarring.

Atopic conjunctivitis typically presents with more severe corneal findings than VKC as many patients can develop corneal neovascularization, scarring, and corneal thinning, however, many of the same features, such as Horner-Trantas dots and giant papillae, are present. Cataract formation can also be seen in AKC as a result of the condition and the chronic use of topical corticosteroids. While VKC often resolves in the second decade of life, AKC often persists throughout life.

Similar to VKC, pathogenesis is primarily immune-mediated with a proliferation of mast cells and eosinophils. Treatment often requires more potent medications including steroids or immunomodulatory agents. The physician may also need to treat eyelid dermatitis. This can be done with application of a low dose topical steroid to the lids two to four times daily. Topical calcineurin inhibitors as mentioned above can be used as an alternative.

Neonatal Conjunctivitis

Case 3 Clinical synopsis: This is a 3-day-old infant who presents with purulent discharge from both eyes. The patient was born at home to a mother with limited prenatal care. The physician was suspicious of *N. gonorrheae* and immediately obtained a Gram stain and culture in Thayer-Martin media as well as on agar plates. The patient was immediately admitted and treated with IV ceftriaxone as well as oral erythromycin to cover any co-infection with chlamydia. Cultures grew *N. gonorrheae*. The infectious disease specialist was consulted to evaluate for any other systemic involvement including septic arthritis. The patient was carefully evaluated for resolution of all ocular symptoms. The mother was educated about sexually transmitted disease and plans were made to test her as well as any sexual partners for STDs including HIV.

Comment Ophthalmia neonatorum is a special name given to conjunctivitis that occurs in infants in the first month of life. It occurs in 1.6–12 % of newborns [22]. Chemical conjunctivitis that results from antimicrobial prophylaxis is the most frequent type of neonatal conjunctivitis.

In the USA, perinatal transmission occurs in 30–40 % of cases from maternal cervical infections [21]. Infants can be infected directly through passage in an infected birth canal during vaginal delivery, or bacterial infections can ascend the birth canal and cause chorioamnionitis and resultant fetal infection. Increased risk factors for this transmission include premature rupture of membranes. The two principal and most severe responsible pathogens are *C. trachomatis* and *N. gonorrheae*. Another pathogen transmitted through direct contact includes Herpes Simplex Virus (HSV). Infected newborn generally present with bilateral purulent discharge within the first 5 days of life.

Common bacteria responsible for neonatal conjunctivitis include *C. trachomatis*, *H. influenza*, and *S. pneumoniae*. Less likely to occur because of prophylaxis, but at high risk of causing severe ocular surface complications is *N. gonorrheae.* Helpful clues to identify the inciting agent are day of onset of conjunctival injection after birth and type of discharge.

Chemical conjunctivitis, characterized by bilateral hyperemia, often occurs within the first day of life, and is a result of antimicrobial prophylaxis used at birth, most often silver nitrate, which fortunately has been mostly abandoned in developed countries. Chemical conjunctivitis is often a self-limited condition.

Gonococcal conjunctivitis, characterized by hyperemia and purulent discharge, often occurs within the first week of life. Although it occurs less frequently, gonococcal conjunctivitis is capable of penetrating the cornea, causing ulceration and perforation. Also concerning is the risk of systemic spread of *Neisseria* and resultant meningitis, sepsis, or arthritis. Topical antibiotics may be helpful in cases of corneal involvement, but otherwise are not indicated. Ocular surface irrigation with saline is also helpful in eliminating the bacteria from the ocular surface.

Chlamydia may present up to 2 weeks after birth and the discharge is frequently described as serous in nature. There may also be edema of the soft tissue (eyelids) and conjunctival chemosis. The conjunctiva may form pseudomembranes that bleed when disrupted. Lack of treatment may result in corneal scarring and cicatrization of the conjunctiva. The diagnosis of *Chlamydia*, an obligate intracellular organism, requires culture of conjunctival scrapings, which can be obtained from an everted eyelid. *Chlamydia* cultures should be sent to the laboratory in 2SP (0.2 M sucrose-phosphate transport medium containing 10 μg of gentamicin/mL, 25 μg of vancomycin/mL, and 25 U of nystatin/mL) if possible. There are more rapid assays for *Chlamydia* and in urgent situations nucleic acid amplification may be acceptable However, in sexual abuse cases, culture is the only acceptable result recognized in by law. Treatment of *Chlamydia* conjunctivitis includes oral erythromycin (50 mg/kg per day PO in four divided doses) for fourteen days per the American Academy of Pediatrics and Centers for Disease Control (CDC). Systemic therapy is indicated to fully treat the patient secondary to risk of *Chlamydia* pneumonitis. Erythromycin is effective in

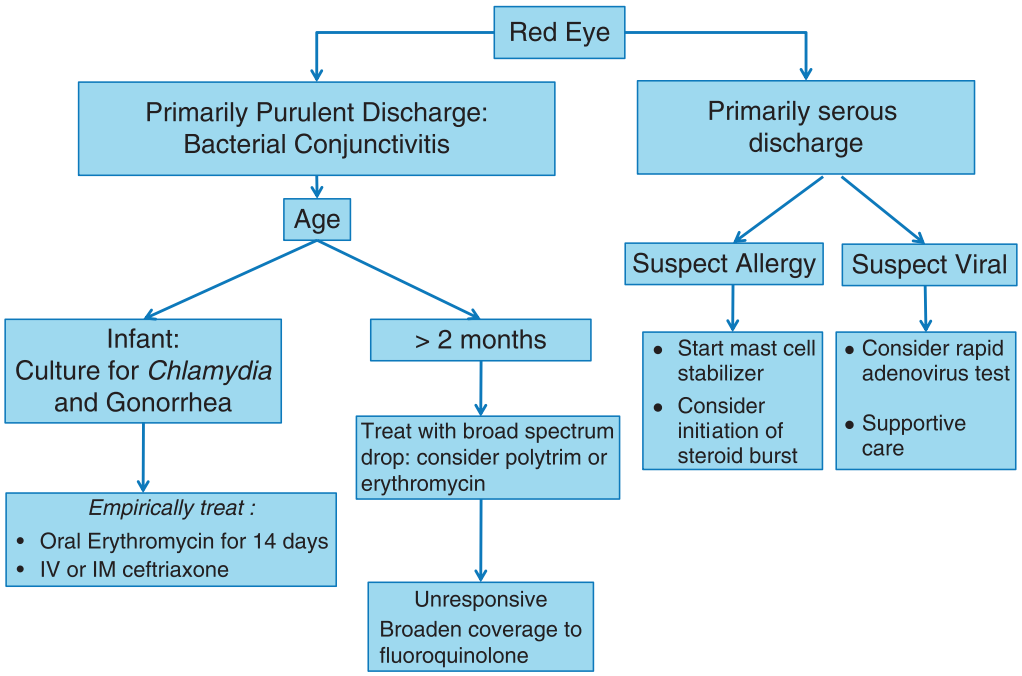

Fig. 1: Red eye flow chart.

only 80–90 % of cases so patients need to be followed closely for complete resolution [22]. The infant's mother and sexual partners need to be evaluated for all STDs including HIV. Co-infection of *Neisseria* and *Chlamydia* is common and infants should be treated for both infections.

The gold standard for diagnosis of gonococcal conjunctivitis is isolation by culture after gram stain. *Neisseria* should be cultured on appropriate selective media (Thayer-Martin or VPN) that inhibit normal flora because they contain antibiotics (vancomycin, colistin, nystatin, and trimethoprim) and facilitate the growth of *Neisseria* species. A diagnosis of gonorrhea mandates hospitalization to evaluate for systemic infection particularly septic arthritis. Treatment should be initiated empirically upon suspicion of infection and consists of a single dose of ceftriaxone (25–50 mg/kg not to exceed 125 mg, IV or IM).

Prophylaxis for neonatal conjunctivitis in the USA is recommended by the American Academy of Pediatrics and Center for Disease Control and Prevention and consists of erythromycin or tetracycline ointment administered to both eyes within 1 h of birth.

See Fig. 1 for red eye flowchart.

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5

Management of Ocular Surface Allergic Diseases

Jeanie Paik, Priti Batta

Case 1

A 5-year-old female presents in the spring with occasional tearing and frequent rubbing of her eyes for 5 weeks. She states her eyes feel itchy. The patient's mother states that the symptoms began at the start of the autumn season and were associated with rhinitis. She has not noticed any deviation of the eyes or difficulty with vision. On exam, the patient's vision is 20/20 in both eyes. She is orthotropic with full motility and gross stereoscopic vision.

What Is Seasonal Allergic Conjunctivitis, and How Does It Typically Present?

Seasonal allergic conjunctivitis is a markedly common allergic eye condition. It is usually a reaction to the presence of environmental allergens in the air, typically plant pollens during the spring and autumn months. Seasonal allergic conjunctivitis is distinguished from perennial allergic conjunctivitis in that the latter is present year-round, resulting in more chronic conjunctival inflammation. Allergic conjunctivitis is a type I immediate IgE-mediated hypersensitivity reaction in which mast cells play a major role. The degranulation of mast cells upon IgE-mediated activation causes the release of histamine, as well as the downstream production of leukotrienes and prostaglandins.

The binding of histamine to H1 and H2 receptors leads to the classic and well-known symptoms of eye allergy: itching, tearing, redness, frequent blinking, conjunctival and eyelid swelling, and mucus production. The symptoms may be quite severe, especially the itching and resultant desire to rub the eyes; this should help to distinguish allergy from other ocular surface conditions such as dry eye syndrome and blepharitis, in which the itching and eye rubbing are usually mild and less frequent. The conjunctival chemosis can be very prominent, creating a "glassy" appearance to the eye, due to sudden severe influx of inflammatory cells into the conjunctiva. Patients

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with chronic ocular allergy often develop eyelid ptosis and wrinkling of the eyelid skin, sometimes with hyperpigmentation, due to repeated bouts of eyelid swelling as well as chronic eye rubbing. The condition is often associated with other manifestations of seasonal allergy such as rhinitis and cough.

Slit-lamp examination commonly reveals papillary changes in the upper and lower tarsus. These are closely packed, flat-topped nodules of the tarsal conjunctival surface, ranging in size and number. Histologic examination of these papillae reveals a central vascular core surrounded by eosinophils and other inflammatory cells.

On slit-lamp exam, the patient has 1+ conjunctival injection in both eyes with boggy conjunctival chemosis. There is no corneal staining. On lid eversion, diffuse, fine papillae are noted on the upper and lower tarsus of both eyes.

Is Any Further Diagnostic Testing Needed? How Would You Manage This Patient?

The diagnosis of seasonal allergic conjunctivitis can typically be made based on clinical history and examination findings. Diagnostic testing is rarely necessary but may be useful in cases that do not seem to respond to medical therapy. A conjunctival scraping may reveal eosinophils which are not normally present in the conjunctiva. However, this is not very sensitive in the diagnosis of allergy, as false negatives are common [1]. Similarly, levels of eosinophil-derived proteins, as well as IgE, are likely to be elevated in the tear film of patients with any form of ocular allergy [2, 3]. However, it does not appear that these levels correlate with disease activity. Serum IgE levels can also be elevated, and these typically correlate with tear film IgE levels [3]. Allergen testing, usually via skin prick testing, may be valuable in guiding treatment by reducing exposures to identifiable allergens. Reducing allergen exposure is often challenging, but when successful, it may be sufficient in controlling the condition. Topical antihistamine eye drops, such as azelastine and epinastine, are very effective in reducing acute allergic symptoms, though they may be inadequate in severe ocular allergy. Similarly, oral antihistamine medications can also be considered, especially if other forms of allergy are also present, such as rhinitis. Topical mast cell stabilizers, such as cromolyn sodium, prevent degranulation of mast cells and therefore reduce both histamine production and the downstream inflammatory mediators. Antihistamines are effective for acute allergy; however mast cell stabilizers are intended for prophylaxis and are appropriate for more chronic cases of ocular allergy. Newer agents have multiple mechanisms of action with both antihistamine and mast cell-stabilizing effects; these include olopatadine, alcaftadine, and ketotifen.

For more severe cases or acute exacerbations, topical corticosteroids may need to be employed. Due to their broader anti-inflammatory activity, they are often highly effective against seasonal allergy, but the significant side effects of cataract and increased intraocular pressure must be considered. The use of topical corticosteroids in ocular allergy should be brief and with the lowest concentration and dosing necessary to achieve control. When possible, milder topical steroids such as loteprednol should be favored over the more potent steroids such as prednisolone acetate.

While nonsteroidal anti-inflammatory medications have been used in the management of allergic disease, we generally do not use these agents and prefer to use more targeted therapies.

In this case, the patient was treated with a combined mast cell stabilizer and antihistamine drop (olopatadine) which effectively controlled her symptoms. If the patient had more allergic rhinitis, then preference would have been given to an oral antihistamine (e.g., loratadine 5–10 mg/day). If the patient was experiencing an acute exacerbation, a short course of loteprednol 0.5% may also be considered at the same time, while the other agent(s) start to work.

Case 2

A 13-year-old male presents with itching of both eyes for several weeks. He also reports light sensitivity with moderate eye pain in his left eye and states that he wakes up with his eyes "stuck together" due to mucus accumulation. He states that for approximately the last 4 years, he has had similar symptoms every year during spring. He is from West Africa and is currently visiting the United States. His family denies any other medical history.

What Is the Typical Clinical History of VKC? How Can the History Help to Differentiate Between VKC and Other Forms of Allergic Eye Disease, Specifically AKC?

Vernal keratoconjunctivitis (VKC) is a bilateral chronic allergic conjunctivitis characterized by itching, foreign body sensation, conjunctival injection and chemosis, photophobia, and filamentous "ropy" mucous discharge [4–6]. The presenting complaints are therefore very similar to AKC, with which it shares many common immunologic mechanisms, and are generally much more severe than seasonal or perennial allergic conjunctivitis.

The disease is termed "vernal" due to its usual presentation during the spring season; however the term is a bit misleading, as some patients with VKC present with year-round symptoms. VKC peaks in the first decade of life and is more commonly seen in boys than girls. It is also more common in hot, dry climates, such as in West Africa or the Middle East [5]. About half of VKC patients have a personal or family history of atopy. In milder cases, VKC is generally a self-limited condition, as it typically resolves by the late teens. However, in some patients, the disease may be more persistent. Importantly, even if the disease becomes quiescent, the long-term sequelae can be lifelong.

In contrast, AKC presents in an older patient population, peaking in the second to fifth decade of life [7]. It has less seasonal variation and geographic specificity than VKC. AKC is much more likely to have a chronic indolent course with greater potential for ocular surface and corneal scarring. AKC patients are more likely to have atopy and have dermatologic disease requiring chronic therapy.

Upon examination, the patient's visual acuity was 20/20 in the right eye and 20/50 in the left. Pupils were equal, round, and reactive. Intraocular pressure was 12 mmHg in both eyes. With lid eversion, giant cobblestone papillae were observed in both upper eyelids (Fig. 1).

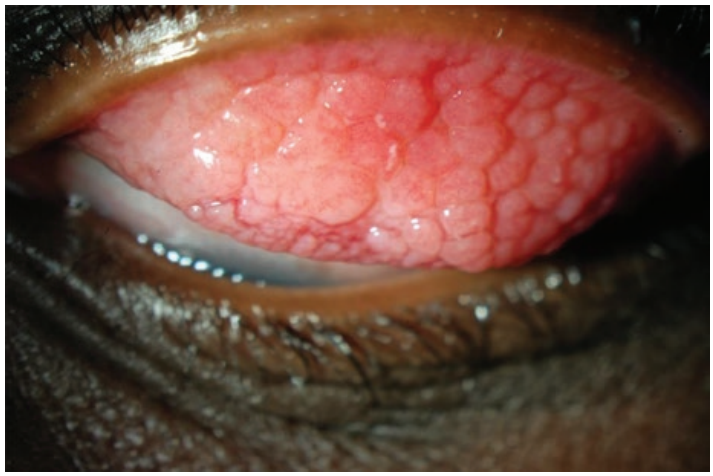


Fig. 1: Giant Papillae in a patient with VKC.

What Are Common Examination Findings in VKC? What Are the Long-Term Sequelae of VKC?

Atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) have similar clinical presentations, with conjunctival hyperemia, papillary reaction, corneal epitheliopathy, and ulceration as common features of each. A trademark feature of VKC is giant "cobblestone" papillae of the upper tarsus; these are less common in AKC. These giant papillae are greater than 1 mm in diameter. A thick ropy discharge frequently accumulates in the septa in between the giant papillae. Limbal papillae may also be seen and are typically large, gelatinous, and confluent. Frequently, either tarsal papillae or limbal papillae predominate, leading to two broad categories of VKC: palpebral vernal and limbal vernal. In the limbal papillae, Horner-Trantas dots may develop, another classic feature of VKC. These are collections of degenerated epithelial debris and eosinophils that form small white dots at the limbus [5, 6].

Patients with VKC almost always have quiet, uninflamed eyelids and periorbital skin, in contrast to the nearly universal presence of periorbital atopic dermatitis seen in AKC patients. Subepithelial fibrosis of the palpebral conjunctiva and symblepharon formation are also much less common in VKC compared to AKC [8]. The mechanical rubbing of giant papillae against the cornea, along with release of inflammatory mediators, contributes to punctate epithelial erosions and sometimes macroerosions. Long-term sequelae of VKC can lead to corneal neovascularization and scarring. A pseudogerontoxon may be seen; this is a linear corneal scar, resembling a partial arcus senilis (gerontoxon). Chronic inflammation may result in severe stromal thinning and even corneal perforation. These findings are not common, and the long-term prognosis for mild VKC is generally good. However, 6% of patients will go on to develop visual impairment secondary to cataract, glaucoma, or corneal damage [4].

Slit-lamp exam revealed a white and quiet right eye and 1+ conjunctival injection in his left eye. His right cornea was clear. His left cornea showed a superior pannus and superficial

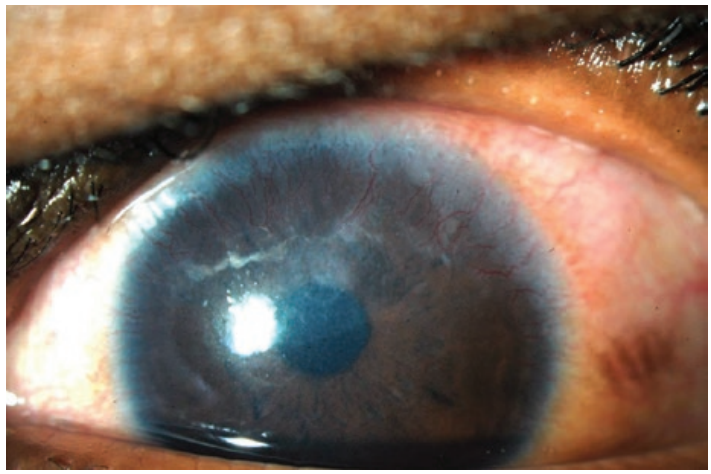


Fig. 2: Superior limbal stem cell deficiency in a patient with chronic VKC.

neovascularization with diffuse, confluent punctate epithelial erosions (Fig. 2). The anterior chamber was deep and quiet in both eyes.

Based on the clinical history and presentation, the patient was diagnosed with VKC.

What Is the Pathophysiology of VKC? What Is Appropriate Medical Management for These Patients?

The pathogenesis of VKC is complex and not entirely understood; a thorough discussion of the immune mechanisms involved is beyond the scope of this chapter. In brief, as with allergic conjunctivitis, eosinophils and mast cells play an important role in VKC, and on cytopathologic examination these cells are seen in the conjunctiva of these patients. However, other inflammatory cells, such as lymphocytes, neutrophils, plasma cells, and macrophages, are clearly involved in VKC, as these are also found in large numbers in the conjunctiva [6]. In particular, T-helper lymphocyte cells (i.e., Th2 cells) are responsible for the production of specific interleukins, such as IL-4 and IL-5, which mediate several of the immune responses in VKC [6]. The production of interleukins and chemokines leads to recruitment of leukocytes, as well as increased production of IgE. Interleukins also promote the proliferation of fibroblasts.

Initial management for VKC is similar to that of other forms of allergic conjunctivitis and should include topical antihistamines and lubrication with artificial tears. Nonsteroidal anti-inflammatory drops may also provide some benefit in symptomatic relief. Mast cell stabilizers and preferably dual-acting agents can be useful for chronic maintenance.

Because of the numerous inflammatory mechanisms involved, these measures are usually inadequate. Topical steroids may be used for exacerbations in moderate to severe VKC and should be used judiciously with close monitoring for side effects. Topical cyclosporine eye drops are highly effective as an adjunctive therapy to decrease chronic inflammation. Cyclosporine has been shown to block T-lymphocyte proliferation, conjunctival fibroblast proliferation, and histamine release from mast cells. The commercially available concentration of 0.05% cyclosporine

(Restasis®, Allergan) can be used up to four times a day, though higher concentrations of 1–2% (compounded) may yield better results. Our standard treatment for these patients is to use topical cyclosporine and a dual-acting antihistamine on a long-term continuous basis. Topical steroids are used for exacerbations and at the lowest effective dose. Topical tacrolimus drops (if available) may be used as an alternative to cyclosporine and likely is more effective given that tacrolimus is 10–100 times more potent than cyclosporine.

Systemic treatment is rarely needed in VKC; however montelukast (Singulair, Merck) has been shown to be effective in reducing symptoms in VKC [9, 10]. Oral antihistamines may have minimal efficacy on VKC but may reduce systemic hyperreactivity. Systemic corticosteroids are rarely necessary but may need to be considered in vision-threatening cases. In cases where systemic steroids are needed, oral tacrolimus is a highly effective steroid-sparing agent which can be used for at least 6–12 months. Comanagement with a pediatric allergist or immunologist is highly recommended in such cases.

Case 3

A 12-year-old male is referred to you by a pediatric ophthalmologist for a chronic corneal ulcer. The child describes severe pain, tearing, and lid swelling of his left eye for approximately 1 month. The parents report that the child has had intermittent itching, tearing, and redness in both eyes for several years. He has been prescribed several different eye drops over the years, with varying **effectiveness. The referral note states that the child had a small corneal ulcer in the same eye approximately 2 years ago, which resolved with topical antibiotics and steroids.**

Is There Any Further History You Would Like to Elicit from the child's family? What Is the Differential Diagnosis of a Chronic Corneal Ulcer in This Patient?

The initial evaluation of a corneal ulcer should differentiate between infectious and noninfectious etiologies. Chronic or recurrent corneal ulceration, along with longstanding symptoms of ocular surface irritation and redness, as in this child's case, points toward an inflammatory cause as the underlying pathology. The differential diagnosis for chronic or recurring corneal ulcer in the pediatric patient includes the following common conditions: atopic and vernal keratoconjunctivitis, staphylococcal blepharitis, ocular rosacea, and herpetic viral keratitis. Pertinent history may include prior episodes of red eye, a history of allergies and/or systemic atopic disease such as eczema and asthma, frequent chalazia or hordeola, history of eyelid blisters or cold sores that may suggest a herpetic etiology, and contact lens wear. It is also important to realize that chronic ocular surface inflammation predisposes the eye to microbial superinfection, and corneal cultures should be considered in all cases of chronic corneal ulceration.

His past medical history is significant only for asthma and allergies, including a severe peanut allergy. He takes oral montelukast and uses an albuterol inhaler as needed for his asthma. He is not currently on any topical medications.

Upon exam, his vision is 20/25 in both eyes. His external lid exam shows moderate swelling of his left upper lid with secondary ptosis (Fig. 3).

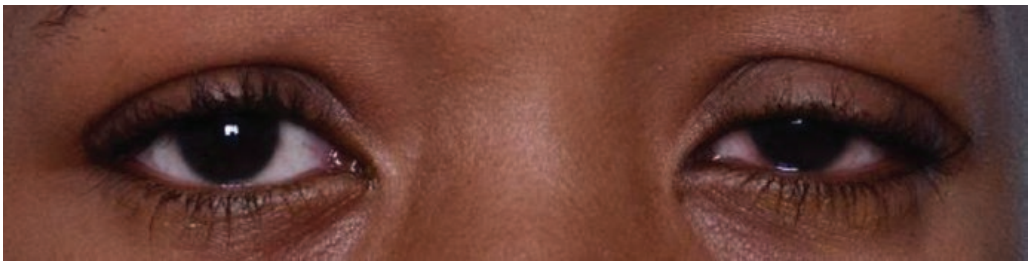
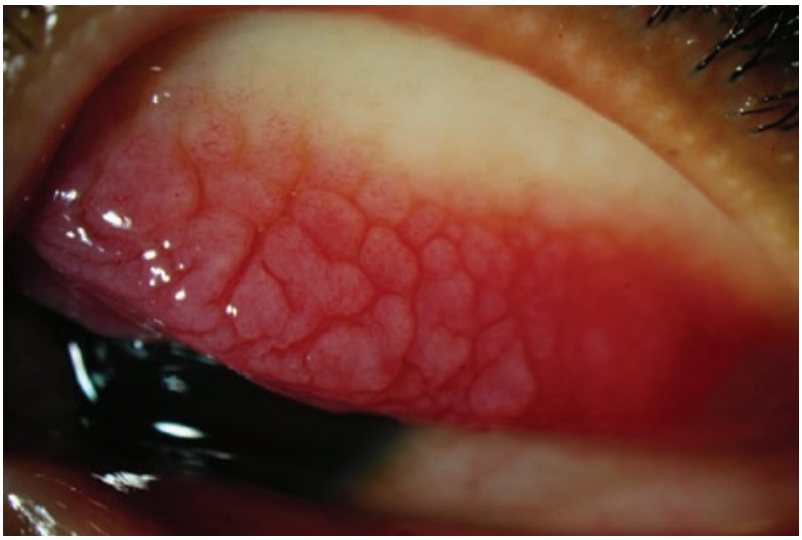


Fig. 3: Moderate swelling of the left upper lid with secondary ptosis in a patient with VKC.

Fig. 4: Giant papillae in a patient with VKC.



Upon lid eversion of his left upper lid revealed giant papillae (Fig. 4).

His corneal exam showed a 2.5 mm × 1 mm corneal "shield" ulcer with a plaque deposit; fluorescein staining revealed extensive filamentary and punctate keratopathy (Fig. 5a, b).

What Is the Pathogenesis of a Shield Ulcer?

Shield ulcers of the cornea may develop secondarily from the mechanical injury from giant papillae, as well as chronic inflammation. Initially, a punctate epithelial keratitis develops which may lead to a frank erosion. Eventually a "vernal" plaque at the level of Bowman's membrane may deposit in these erosions, referred to as a shield ulcer due to its appearance. These are adherent mucus plaques consisting of degraded epithelial cells, eosinophils, and inflammatory cells. The incidence of shield ulcers in VKC has been reported from 3 to 11% [4, 6, 11]. They are typically localized to the superior half of the cornea, which underlies the tarsal papillae. The plaque

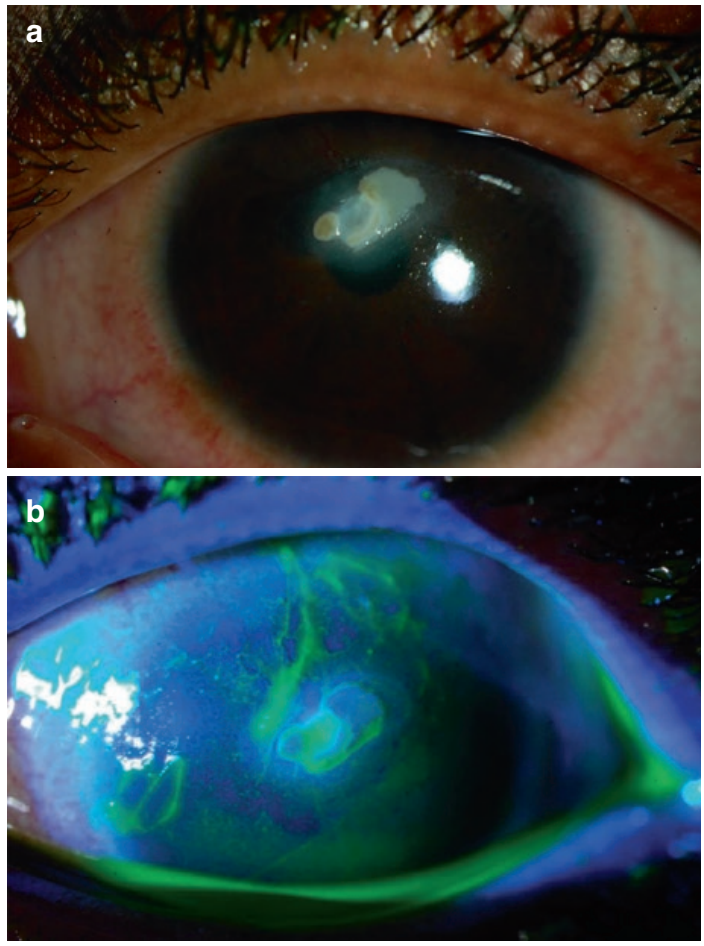


Fig. 5: Typical central shield ulcer with a plaque in a patient with VKC (**a** and **b**).

impedes epithelial healing, and chronic shield ulcers may result in corneal scarring, neovascularization, and stromal thinning.

The patient was diagnosed with VKC and the edges of the shield ulcer were cultured. The patient was started on moxifloxacin four times a day in the left eye and olopatadine 0.1% in both eyes two times a day. The culture had no growth at follow-up. The patient was then started on loteprednol (Lotemax, Bausch & Lomb) four times a day in the left eye.

How Should Shield Ulcers Initially Be Managed?

Shield ulcers can often be difficult to treat and may follow a chronic or relapsing course. Topical steroids should be employed to reduce surface inflammation contributing to plaque deposition, and topical antibiotics should be administered for prophylaxis. After the eye drop regimen has been optimized, debridement of the shield ulcer manually or with the use of phototherapeutic keratectomy can be attempted to stimulate re-epithelization [12, 13]. If the epithelial defect

persists, surface treatments such as a bandage contact lens and amniotic membrane transplant can be considered.

The shield ulcer and papillae remained unchanged on topical therapy at the patient's next follow-up 2 weeks later, though his symptoms of itching and pain were improved. Debridement of the plaque was performed with eventual recurrence of his shield ulcer on further follow-up.

What Are Some Other Treatment Options for Recalcitrant Shield Ulcers?

The size of the giant papillae has been directly correlated with the persistence or worsening of symptoms [4]. In retrospect, loteprednol was likely inadequate, and more potent steroids (e.g., prednisolone acetate 1% every 2 h) may have been more effective at reducing the inflammation for our patient. Alternatively, a supratarsal injection of steroids can be considered in cases of shield ulcer unresponsive to medical therapy, both to reduce the size of the giant papillae (thereby relieving the mechanical corneal irritation) and to decrease the number of inflammatory mediators on the ocular surface [14, 15]. Multiple injections may be needed. The patient should also be treated with topical cyclosporine on a long-term basis.

Case 4

A 27-year-old male presents with decreased vision in both eyes for 5 years. He also reports a chronically itchy rash around his eyes. His medical history is significant for eczema, asthma, and allergies since childhood.

His visual acuity at presentation was 20/200 and 20/40, respectively. The external lid exam revealed an excoriated, scaly periorbital dermatitis (Fig. 6). and inspissated meibomian

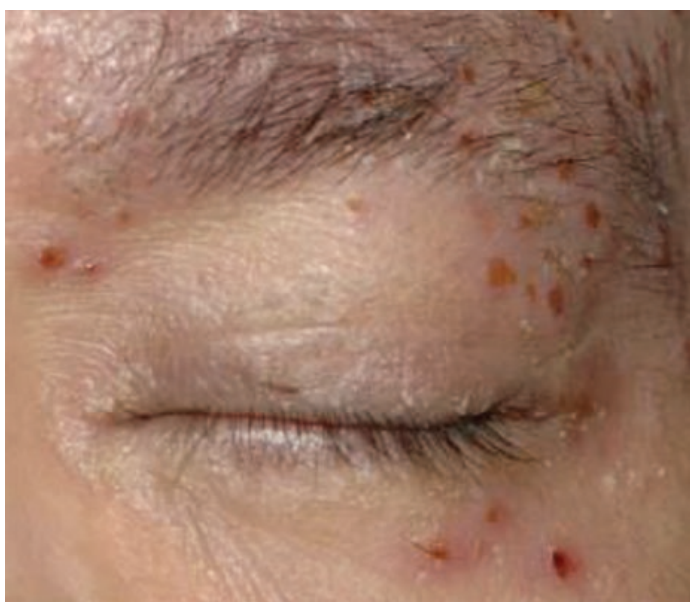


Fig. 6: Skin changes in a patient with AKC.

glands with thickened lid margins. Upon lid eversion, diffuse micropapillae were noted on the upper and lower tarsus.

What Is the Typical Clinical History of Patients with AKC? What Are Common Skin and Eyelid Findings in AKC?

Of the diseases in the allergic spectrum, AKC has the most severe, chronic course marked by significant ocular morbidity from corneal and conjunctival scarring. A thorough medical history should be obtained. Of AKC patients, 95% have concurrent eczematous dermatitis [8, 16, 17]. Other common associations include asthma and allergies, seen in up to 65–87% of patients [8, 16, 18]. AKC patients commonly present in the third to fifth decades [7]. Unlike VKC, AKC often persists, and patients may need lifelong treatment.

Clinically, AKC presents with chronic, erythematous itchy eyes with tearing [19, 20]. Pain is rarely reported; however the patient may have ocular irritation with photophobia. The external eyelid exam often reveals wrinkled, flaky, excoriated periorbital skin classic for eczematous dermatitis. Other signs include Dennie-Morgan folds, which are additional linear creases of the lower lids secondary to edema and eyelid thickening, and de Hertoghe sign, referring to the loss of hairs in the outer third of the brow [21]. Vertical corrugations near the medial canthus of the upper and lower lids may be seen. With progression of eczema, fissuring of the skin can be seen, and in long-standing AKC, ectropion, ptosis, lagophthalmos, and madarosis may result.

The patient's slit-lamp exam was significant for boggy chemotic conjunctiva and 1+ injection in both eyes. He had diffuse punctate epithelial erosions, central corneal steepening with apical scarring, and a positive Munson's sign in his right eye. The anterior chamber was deep and quiet in both eyes.

How Does AKC Affect the Conjunctiva and Cornea? What Are Other Ocular Associations Seen in AKC?

As in VKC, papillary hypertrophy is prominent, though the conjunctival papillae in AKC preferentially involve the lower tarsus and are smaller than those seen in VKC. The conjunctiva is inflamed and chemotic, though limbal papillae and Horner Trantas dots are less common. Punctate epithelial erosions and corneal hypoesthesia in the setting of a poor ocular surface may lead to macroerosions. As in VKC, shield ulcers with plaque formation can develop.

Of all the allergic eye diseases, AKC is the most chronic and difficult to control, and patients often exhibit the usual complications of persistent ocular surface inflammation. Subepithelial fibrosis may occur with long-term disease, and endstage cicatricial changes include symblepharon formation and fornix foreshortening [22]. Mechanical surface irritation and chronic inflammation can result in limbal stem cell deficiency. Late-stage corneal involvement including limbal stem cell deficiency, neovascularization, pseudopterygium, subepithelial haze, and stromal scarring and thinning can be seen in 60–70% of patients, leading to visual debilitation and even blindness [18, 22]. Approximately 30–50% of these patients require penetrating keratoplasty for visual rehabilitation or tectonic support [18].

Cataract develops early in these patients and usually presents as anterior subcapsular changes in a stellate or shield-like pattern. Posterior subcapsular cataracts can develop secondarily from chronic steroid use. HSV keratitis is more common in these patients due to underlying immune dysfunction and may manifest as a bilateral keratitis. There is a known association of AKC with keratoconus and pellucid marginal degeneration, which may be partly related to excessive eye rubbing [23, 24]. In this particular patient, the keratoconus was more advanced in his right eye which correlated with the side of his hand dominance [25]. There is also a higher observed rate of retinal detachment in AKC patients which may be due to vitreous degeneration from eye rubbing [26]. These patients also appear to be at higher risk for developing glaucoma which may be exacerbated by the chronic use of topical steroids.

The patient was prescribed topical tacrolimus ointment for the eyelid skin and olopatadine eye drops in both eyes twice daily. Lid hygiene and warm compresses were suggested, as well as frequent lubrication with artificial tears. The patient was also referred to an allergist.

What Is the Treatment Approach to AKC?

Treatment goals include controlling ocular inflammation and preventing visual debilitation while using the lowest dose and safest medications possible. A multidisciplinary team is needed including allergists and dermatologists. Improving atopic dermatitis lid disease can secondarily improve the ocular surface in AKC. Daily lid hygiene with warm compresses and lid scrubs should be initiated to control any meibomian gland dysfunction and staphylococcal colonization which can exacerbate surface inflammation. Periocular eczema can be controlled with topical emollients and, as needed, mild topical steroid ointments and emollients [27]. If steroid side effects are a concern, steroid-sparing ointments can be considered. Tacrolimus (Protopic, Astellas) is a calcineurin inhibitor that, like cyclosporine, leads to decreased T-cell production, inhibiting the release of interleukin-2. Compared to cyclosporine, tacrolimus is a more potent immunosuppressant and inhibitor of IgE-mediated enzyme release [21, 28]. Tacrolimus is available as a 0.03% and 0.1% topical ointment and has been shown to be effective in treating atopic lid disease as a steroid-sparing immunosuppressive. An ophthalmic preparation of tacrolimus is not available (except by compounding), but studies have reported symptomatic improvement with off-label ophthalmic use of the ointment in the conjunctival sac and topical use on the external lids with presumed ocular spillover [28, 29].

For conjunctival symptoms, we prefer to start with a combination of mast cell stabilizer and H1 receptor inhibitor (olopatadine, ketotifen, azelastine) to help reduce itch symptoms and overall decrease eye rubbing. As with VKC, cyclosporine may be effective in controlling T-cell-mediated inflammation. Cyclosporine 0.05% (Restasis®, Allergan) has been studied in a small number of AKC patients in two randomized controlled trials; a 2004 study showed improvement of signs and symptoms of AKC [30], and a more recent study showed no statistical difference with placebo in steroid-dependent AKC [31]. Cyclosporine 0.05% (Restasis®) or compounded 1–2% is recommended in all AKC patients. Clinical experience has shown topical T-cell inhibitors (cyclosporine or tacrolimus) to be extremely effective in all patients with chronic allergic eye disease and are recommended as a long-term treatment in every case. More severe AKC will require

topical steroids such as prednisolone acetate 1% or difluprednate 0.05% with gradual tapering to more mild topical steroids (loteprednol or fluorometholone) as ocular inflammation is controlled. Prudent short-term use of steroids should be utilized to reduce long-term effects of cataract and glaucoma. It is well known that patients with AKC are at higher risk of developing herpetic keratitis, and AKC is a frequent cause of bilateral HSV keratitis. Thus, patients on chronic steroids are monitored for reactivation of HSV. Finally, in our experience, patients with AKC tend to be more sensitive to BAK; therefore, preservative-free or non-BAK preserved drops may be preferred whenever possible.

Systemic antihistamine may be used in addition to topical therapy and may provide additional anti-inflammatory effect. However, for severe refractory AKC, we prefer to use systemic immunosuppression with oral agents particularly cyclosporine or preferably tacrolimus. These agents have been found to be extremely effective and should be considered in all patients with ongoing inflammation and vision-threatening disease despite topical therapy [27, 32]. More recently, the use of anti-IgE (omalizumab) has been reported for the treatment of AKC, but experience is very limited [33].

At a follow-up visit 3 weeks later, the patient had mild improvement of his symptoms; however his clinical exam was unchanged. Cyclosporine 0.05% (Restasis®, Allergan) four times a day in both eyes and tobramycin/dexamethasone ointment (Tobradex, Alcon) to the lid margin three times a day in both eyes were added to his regimen with the plan to transition to topical tacrolimus ointment (0.03%). An extensive discussion with the patient stressed the need for optimization of the ocular surface and his disease prior to keratoplasty for his keratoconus.

What Are Some Considerations When Planning Penetrating Keratoplasty in AKC Patients?

Penetrating keratoplasty in AKC patients is associated with higher rates of graft failure. The risk of graft rejection is relatively high, not only because of ocular surface inflammation and corneal neovascularization but also due to the underlying systemic immune dysregulation in atopic patients. Reports suggest that patients with higher serum IgE levels have increased risk of corneal graft rejection [25]. Penetrating keratoplasty in AKC may also stimulate further ocular surface inflammation, worsening the atopic disease. This is known as post-keratoplasty atopic keratitis [34]. A persistent epithelial defect is more likely to occur, due to limbal stem cell deficiency and irregular corneal epithelium.

It is important to optimize the ocular surface and minimize inflammation prior to keratoplasty. Ideally a keratoplasty should only be considered when the ocular surface inflammation is under control. If keratoplasty cannot be avoided in a patient with severely active AKC, then systemic immune suppression should be strongly considered, starting several weeks to months before surgery. The quality of the tear film should be optimized with appropriate agents recommended to treat blepharitis, meibomian gland dysfunction, and tear deficiency. Amniotic membrane transplantation can be considered at the time of keratoplasty to reduce the chances of persistent epithelial defect in patients. Additionally, atopies tend to be eye rubbers, and the importance of

refraining from this after keratoplasty should be clearly conveyed to patients. Finally, limbal stem cell deficiency is a long-term complication of AKC (and VKC), and therefore management of LSCD (e.g., through limbal transplantation) may be indicated prior to keratoplasty (Fig. 7).

Summary

Allergic eye disease includes several conditions that vary in clinical presentation and severity. Common among all allergic eye diseases is a type I hypersensitivity reaction to antigens, mediated by IgE, which leads to mast cell degranulation and histamine release. In vernal and atopic keratoconjunctivitis, T-cell activation plays a prominent role. In all forms of ocular allergy, topical antihistamines/mast cell stabilizers are a mainstay of treatment, with topical steroids reserved for exacerbations. The topical T-cell inhibitors, cyclosporine and tacrolimus, are very effective and are recommended for all patients requiring long-term therapy. Chronic allergic eye disease can lead to conjunctival and corneal scarring, resulting in significant visual impairment. In addition

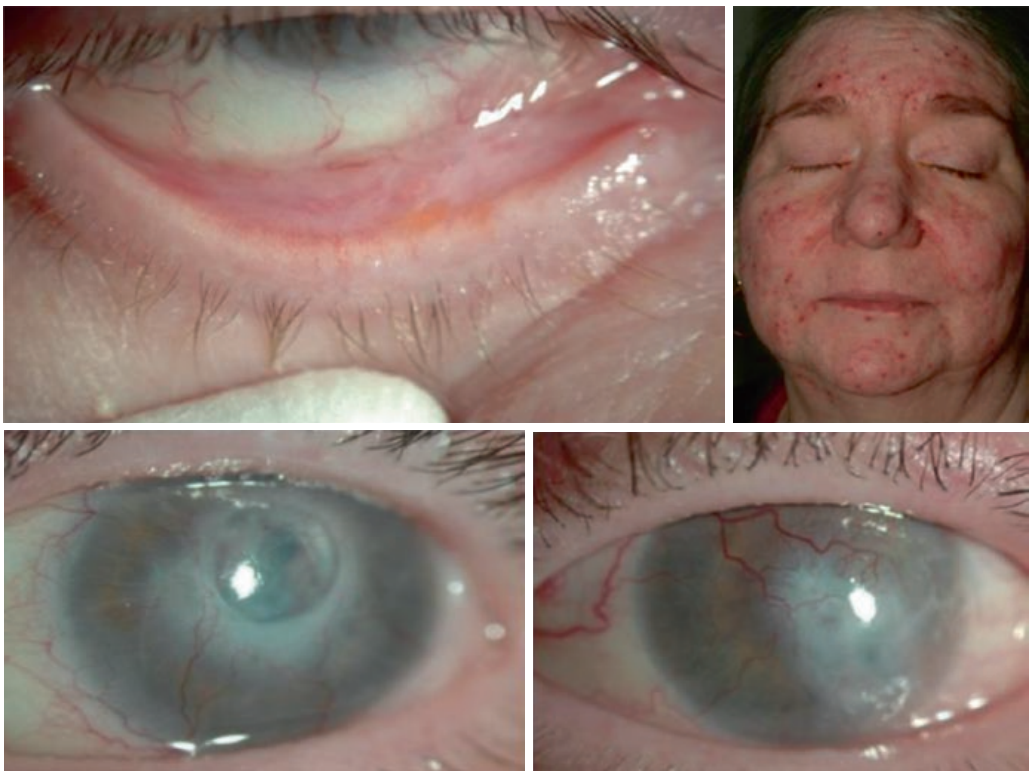


Fig. 7: Patient with chronic AKC leading to conjunctival scarring and bilateral limbal stem cell deficiency. Patient had a history of recurrent epithelial defects and corneal perforation requiring patch grafting. The patient later underwent limbal stem cell transplantation and penetrating keratoplasty.

to corneal complications such as shield ulcers, patients with long-standing disease often develop limbal stem cell deficiency and corneal scarring from chronic AKC suggesting that earlier intervention with T-cell inhibitors (cyclosporine or tacrolimus) topically and perhaps systemically (for the most severe cases) could have prevented these devastating long-term complications (Fig. 7).

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Notes:

In Allergic Conjunctivitis

Rx Combipat

Ketorolac tromethamine 0.4% + Olopatadine 0.1% Ophthalmic Solution

Combined to Combat Allergy

- Synergistic action for complete control[1]
- Effectively relieves itching, hyperemia & chemosis[1]
- Excellent Tolerability[1]

Goodbye Allergy, Hello Relief

1. United States Patent Application Publications: Pub No. US 2013/0281506 A1; Combination of a non-Steroidal anti-inflamatory drug with an anti-histaminic drug intended for ophthalmic use

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