DIAGNOSING AND MANAGEMENT OF CHRONIC ALLERGIC CONJUNCTITIS

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Chronic allergic conjunctivitis

- The ocular surface may exhibit a wide variety of immunologic responses that may result in conjunctival and corneal inflammation
- Sub-types
  - Vernal kerato-conjunctivitis
  - Atopic kerato-conjunctivitis
  - Giant papillary conjunctivitis
- Diagnosis of allergic conjunctivitis generally is made by taking a thorough history and by careful clinical

VERNAL KERATOCONJUNCTIVITIS

- VKC is a chronic bilateral inflammation of the conjunctiva
- commonly associated with a personal and/or family history of atopy.
- More than 90% of patients exhibit one or more atopic conditions, such as asthma, eczema, or seasonal allergic rhinitis.
- dry and hot climates.
- M:F=4:1
- onset before 10 years. The earliest reported onset is 5 months .
- Usually resolves after puberty (around 4–10 years after onset)
- ? Genetic and hormonal predisposition

ATOPIC KERATOCONJUNCTIVITIS

- AKC is a bilateral inflammation of conjunctiva and eyelids,
- has a strong association with atopic dermatitis.
- A type I hypersensitivity disorder with many similarities to VKC, yet distinct .
- Atopic dermatitis is a common hereditary disorder that usually has its onset in childhood; symptoms may regress with advancing age. 25% have ocular involvement

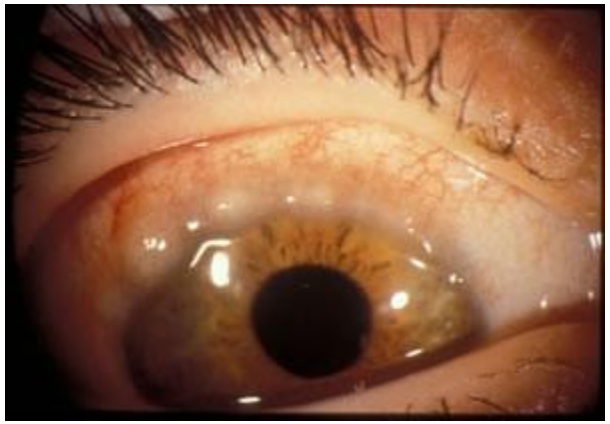
GIANT PAPILLARY CONJUNCTIVITIS

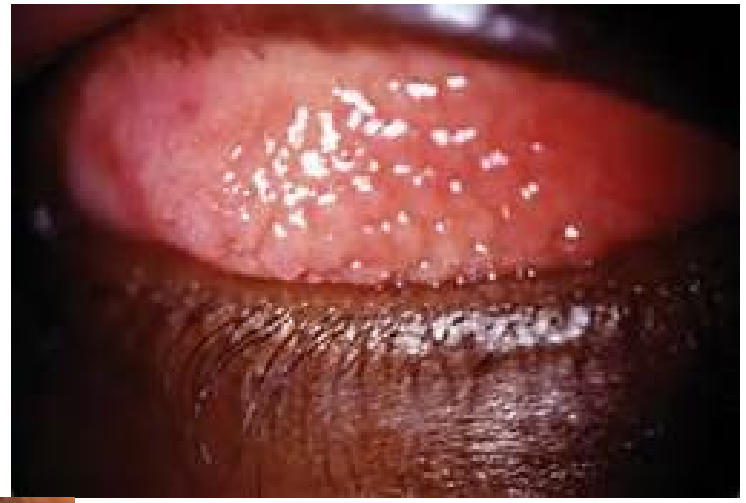
- GPC is an immune-mediated inflammatory disorder of superior tarsal conjunctiva.
- the primary finding is the presence of "giant" papillae, which are typically greater than 0.3 mm in diameter.
- A combination of type I and type IV hypersensitivity reactions may be responsible for the pathogenesis of GPC.
- The stimulus for development of GPC is an immunologic reaction to a specific antigen in predisposed individuals.
- Prolonged mechanical irritation to the superior tarsal conjunctiva from foreign bodies on the ocular surface
- Contact lenses (hard and soft) are the most common irritant.
- Others- ocular prostheses, extruded scleral buckles, and exposed sutures

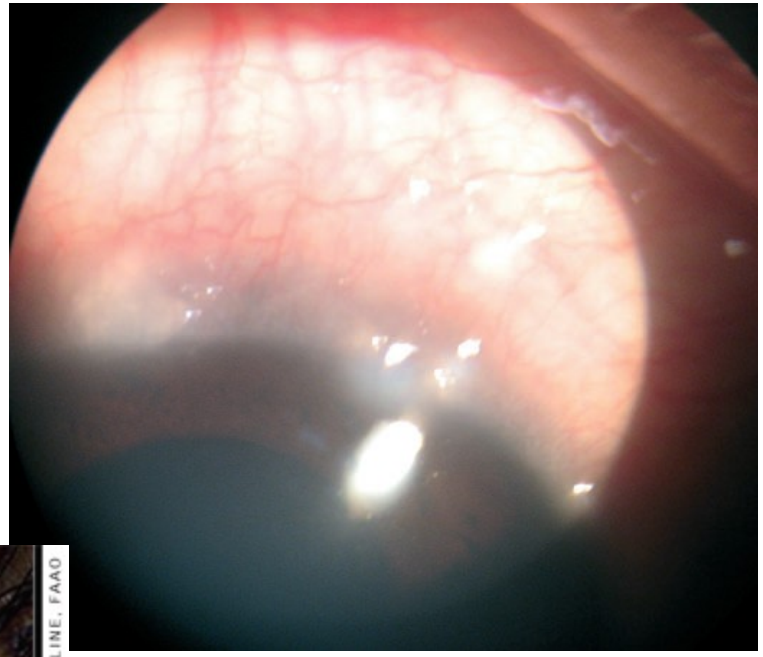
CLINICAL FINDINGS-VCK

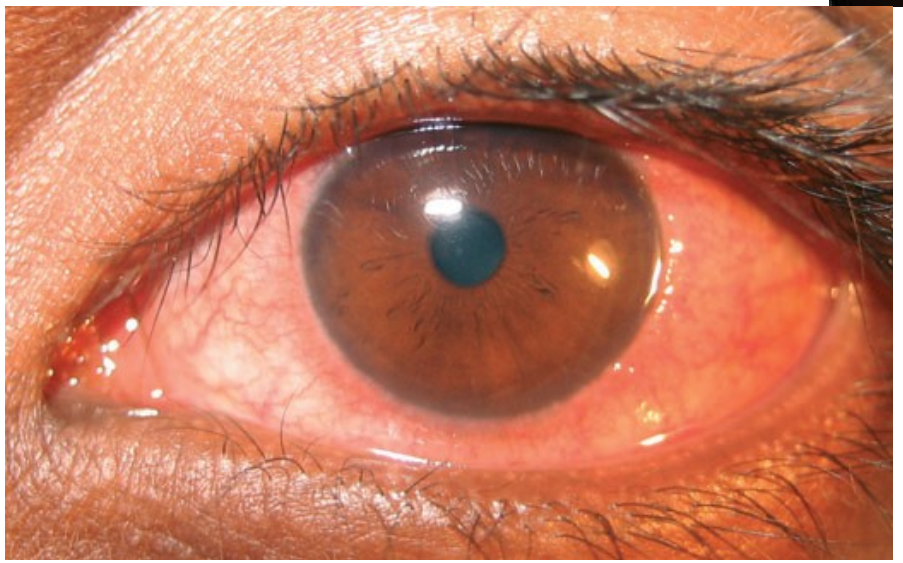
- The classic conjunctival sign in palpebral VKC is the presence of giant papillae. They most commonly occur on the superior tarsal conjunctiva; usually, the inferior tarsal conjunctiva is unaffected.
- 3 clinical types: palpebral limbal and mixed.
  - The limbal form :
    - occurs in dark-skinned individuals.
    - papillae tend to occur at the limbus and have a thick gelatinous appearance.
    - associated with multiple white spots (Horner-Trantas dots)- collections of degenerated epithelial cells and eosinophils; transient and recurrent.
  - Palpebral
    - Papillae size correlate positively with the persistence or worsening of symptoms over long-term. Papillae that may attain a size of 7–8 mm are known as cobblestone They become quite swollen during the active stage but persist even during the quiescent stage. In severe cases, large papillae may cause mechanical ptosis.
- A ropy mucous discharge containing large numbers of eosinophils, is commonly associated with tarsal papillae.
- Perilimbal conjunctival pigmentation has been reported to be a constant finding.

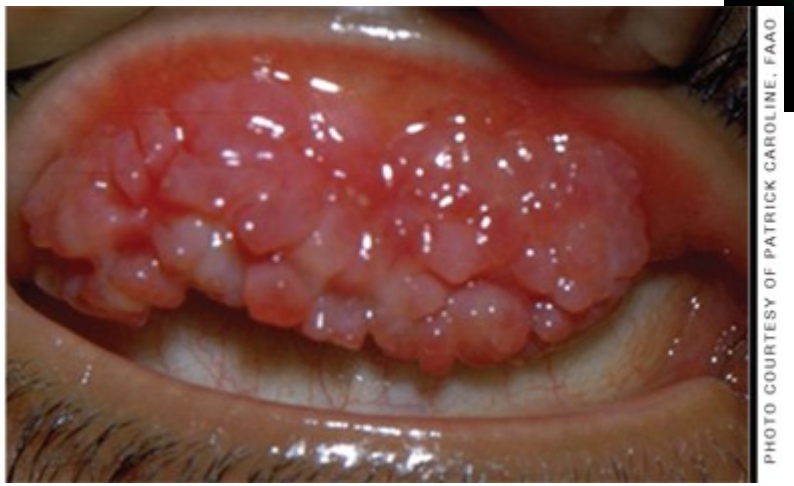
CLINICAL FINDINGS-VCK











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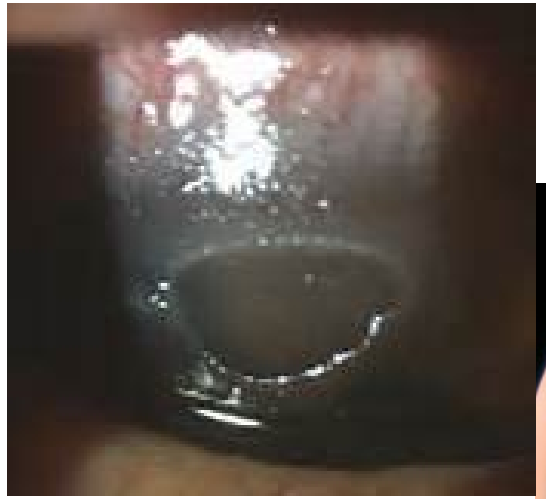
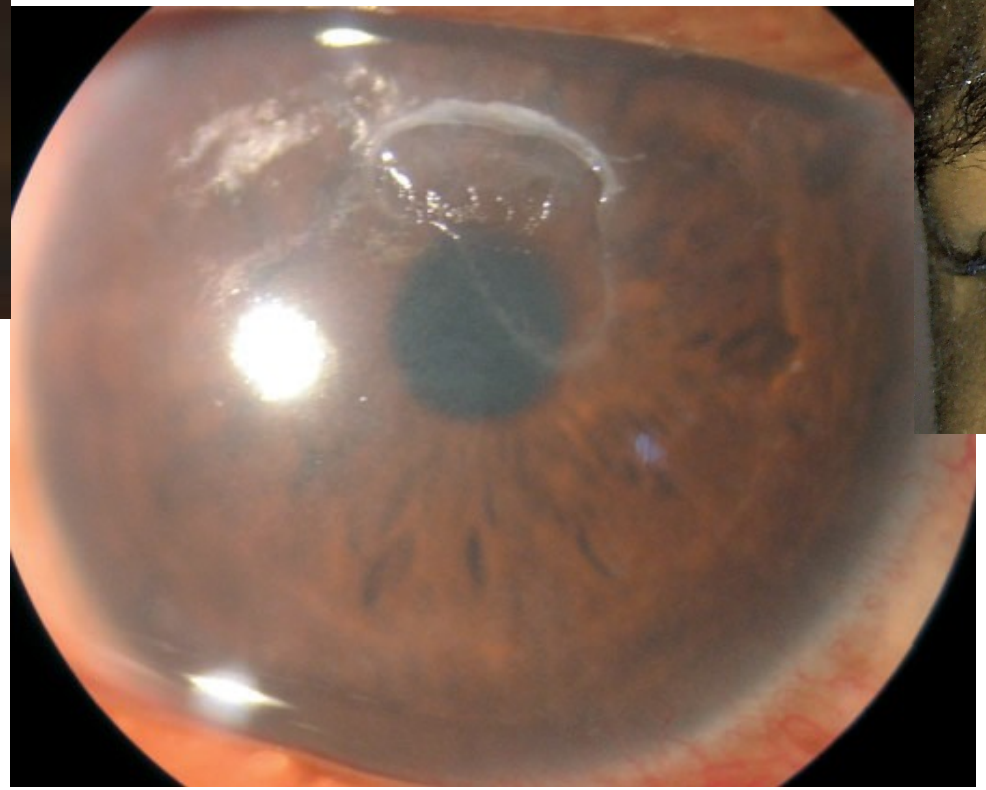
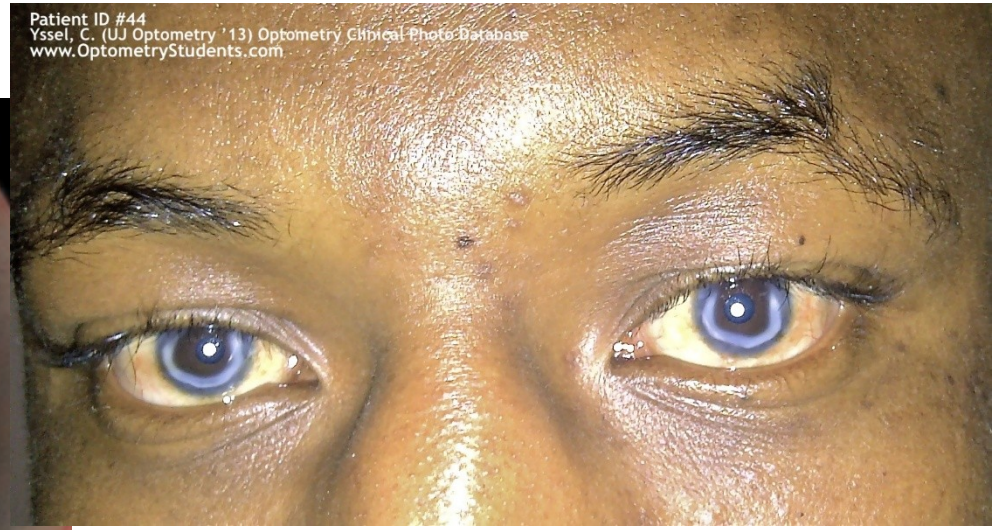
Corneal involvement in VKC

- Photophobia, pain and foreign body sensation are symptoms of corneal involvement.
- Corneal changes include
  - punctate epithelial keratitis = coalesce= epithelial macro-erosions (shield ulcers)= plaque containing fibrin and mucus deposits over the epithelial defect impairing healing = new vessel in-growth
  - Healed shield ulcers may leave a subepithelial ring-like scar
  - Factors involved in promoting development of shield ulcers include chronic mechanical irritation from the giant tarsal papillae and substances released from eosinophils.
  - Vernal pseudogerontoxon is a degenerative lesion in the peripheral cornea resembling corneal arcus.
  - Keratoconus may be seen in chronic cases
    - may be associated with chronic eye rubbing.

Corneal involvement in VKC







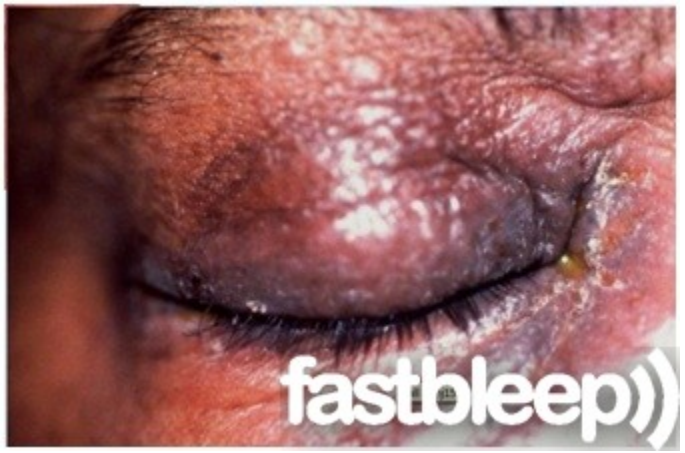
Atopic keratoconjunctivitis- clinical features

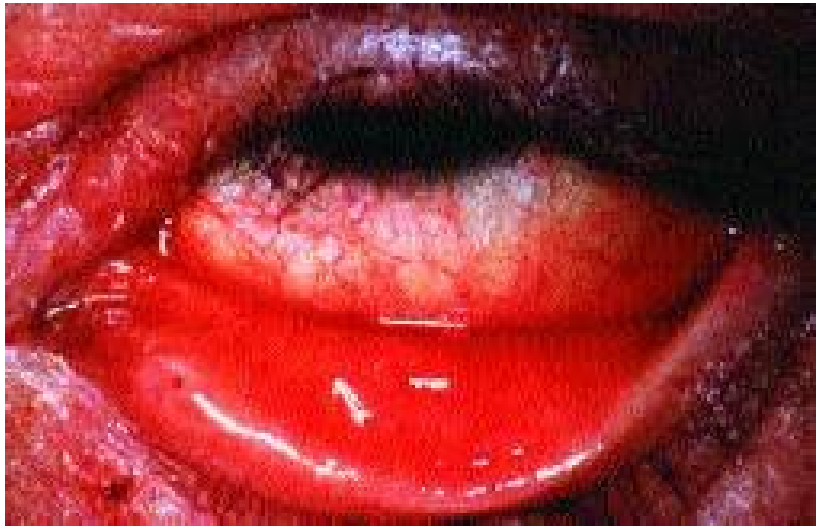
- AKC may affect eyelid skin and lid margin, conjunctiva, cornea, and lens.
- Skin of the eyelids may exhibit eczematoid dermatitis with dry, scaly, and inflamed skin.
- Lid margins may show meibomian gland dysfunction and keratinization. Staphylococcal colonization of eyelid margins is very common and may result in blepharitis.
- Conjunctiva may show chemosis and typically a papillary reaction, which is more prominent in the inferior tarsal conjunctiva.
- Limbal conjunctival hyperplasi and Horner-Trantas dots also may be present but rare.
- Fibrosis or scarring of the conjunctiva may result in a shortened fornix or symblepharon formation with chronic inflammation.

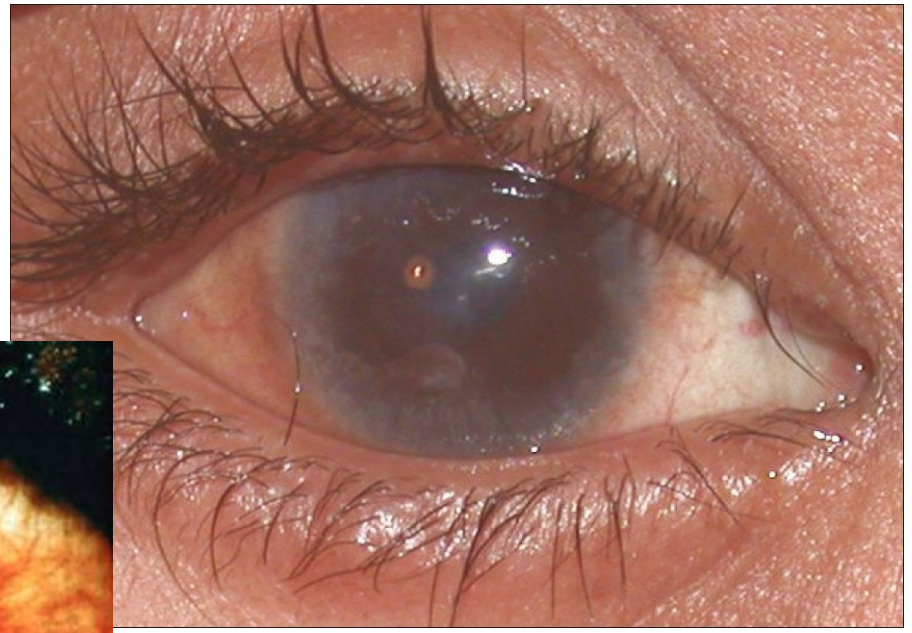
Other ocular involvement in AKC

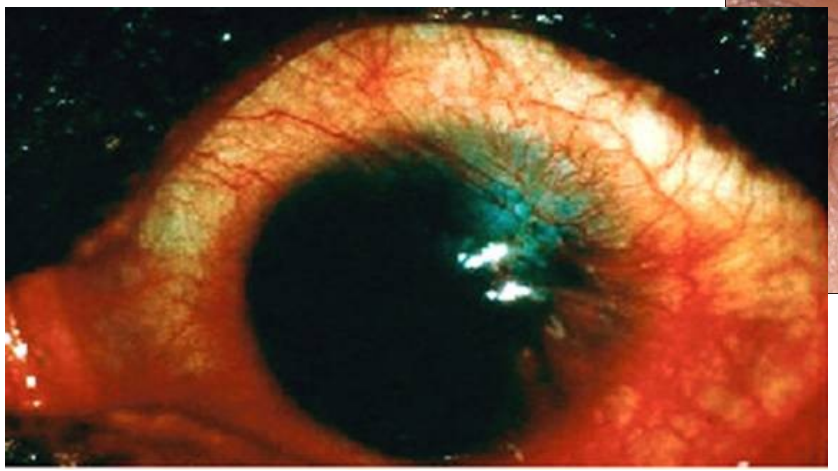
- Corneal involvement
  - punctate epithelial keratopathy occurs early in the course of the disease
  - Neovascularization, stromal ulceration and scarring.
  - There is a strong association between herpes simplex viral keratitis and AKC.
  - Keratoconus from chronic eye rubbing.
- Characteristic lenticular changes - bilateral anterior or posterior subcapsular cataract usually presenting in the second decade of life but progress very slowly.
  - May be associated with the long-term use of topical corticosteroids.
- Increased incidence of retinal detachment following surgical removal of cataracts in patients with atopic dermatitis.

Atopic keratoconjunctivitis- clinical features









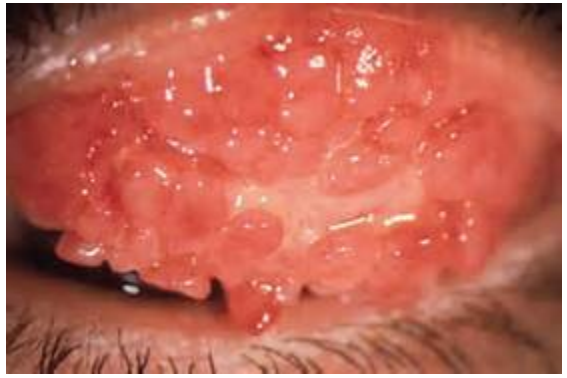
Factors involved in corneal disease

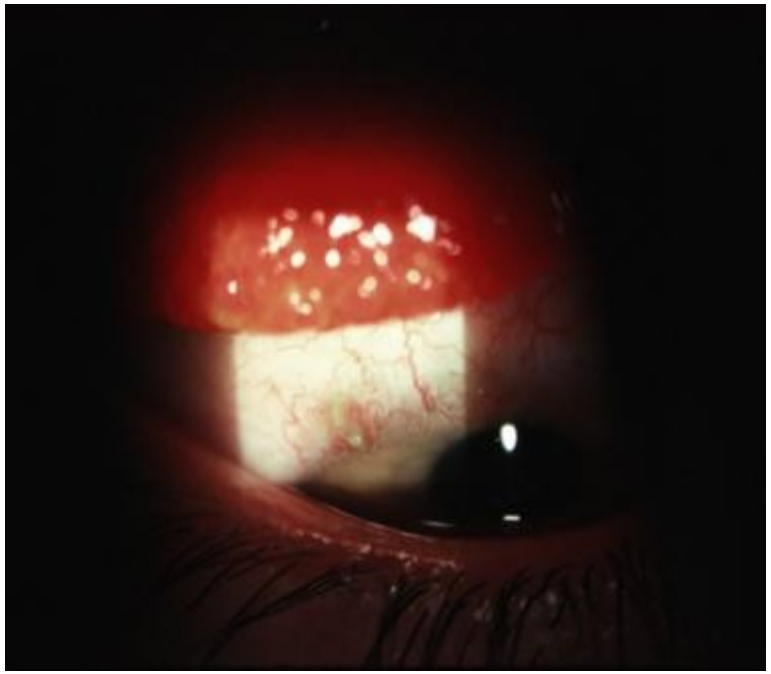
- **Inflammatory Cells in the Tear Film**
  - In patients with severe allergic eye disease, the cellular constitution of the tear film changes with increased eosinophils and lymphocytes.
- **Tear Film Instability**
  - goblet cell loss and conjunctival squamous metaplasia
- **Corneal Sensitivity**
  - Atopic keratoconjunctivitis is associated with a reduction in corneal sensation
  - Loss of corneal sensitivity in itself can lead to corneal disease and ulceration.
  - May be mediated by anatomical changes in corneal nerves or by inflammatory infiltrates along the nerves

Giant papillary conjunctivitis - clinical features

- Examination of superior tarsal conjunctiva reveals the presence of large cobblestone papillae, which are generally 0.3 mm or greater in diameter and, in severe cases, may cause mechanical ptosis of the upper lid.
- In his original description of GPC in 1977, Allansmith described 3 zones of superior tarsal conjunctiva.
  - Zone 1 is located closest to the fornix and is the most inferior portion of the tarsal conjunctiva seen when the upper eyelid is everted.
  - Zone 3 is located closest to the eyelid margin.
  - Zone 2 is located between zone 1 and zone 3.
- Papillae typically associated with soft contact lens–related GPC initially appear in zone 1 and progress toward zone 3,
- papillae associated with rigid gas permeable contact lenses exhibit a reverse pattern, with zone 3 affected first.
- GPC associated with a localized irritant, such as an exposed suture or a filtering bleb, is typically localized to the area overlying these inciting lesions.
- Chronic bulbar conjunctival injection and inflammation due to prolonged and persistent use of contact lenses may be present

Giant papillary conjunctivitis - clinical features





Major Differentiating Factors Between VKC and AKC

- Corneal neovascularization is rare in VKC
- Signs of VKC are confined mostly to the conjunctiva and cornea.
- Papillae are rare in the inferior fornix
- The skin of the lid and lid margin are relatively uninvolved.
- The conjunctiva of the fornices does not usually show foreshortening and symblepharon formation.
- Dry eye syndrome, reported in patients suffering from VKC, may be caused by unsupervised use of topical corticosteroids

ajor Differentiating Factors Between VKC and AKC

Characteristics	VKC	AKC
Age at onset	Generally presents at a younger age than AKC	-
Sex	Males are affected preferentially.	No sex predilection
Seasonal variation	Typically occurs during spring months	Generally perennial
Discharge	Thick mucoid discharge	Watery and clear discharge
Conjunctival scarring	-	Higher incidence of conjunctival scarring
Horner-Trantas dots	Horner-Trantas dots and shield ulcers are commonly seen.	Presence of Horner-Trantas dots is rare.
Corneal neovascularization	Not present	Deep corneal neovascularization tends to develop
Presence of eosinophils in conjunctival scraping	Conjunctival scraping reveals eosinophils to a greater degree in VKC than in AKC	Presence of eosinophils is less likely

Corneal involvement in ocular allergy

Corneal signs	VKC	AKC
Tranta's dots	++	±
SPK	+	+
Ulcer	++	+
Plaques	+	+
Neovascularization	+	+++
Pseudogerontoxon	+	±
Keratoconus	+	++
Scars	+	+++
Stem cell deficiency	+	+
Infections	±	+†

Rx - Preventive measures and patient education

- Compliance with instructions is better with a well-informed patient and outcome of treatment is gratifying.
- Education of patients and their parents about the chronic, recurrent and ultimately resolving nature of ds is very important.
- exposure to non-specific stimuli causes frequent conjunctival redness therefore avoidance of triggering factors like sun, wind and salt water.
- Contact with commonly known allergens like plants and flowers should be avoided.
- Use of sunglasses is helpful and should be advised.
- Application of cold compresses provide symptomatic relief, especially from ocular pruritus
- use of arti-ficial tears have been shown to be effective in the relief of symptoms by direct removal and dilution of allergen from the ocular surface.
- Frequent hand, face and hair washing, especially before going to bed, may be helpful

Pharmacological therapy

- Most drugs used are merely palliative and do not eliminate the causative complex immune response
- Therefore there is recurrence of disease when the therapy is discontinued.
- Drug treatment is prolonged, sometimes perennial and frequent therefore choice and monitoring essential.
- Available medication include: Anti-histamines, Mast-cell stabilizers, Dual acting agents, Corticosteroids Immunomodulators

Suggested Drug Treatment

- An assessment of the efficacy of currently available topical drugs for VKC through a meta-analysis of randomized clinical trials published up to December 2005
  - while treatment worked, there was a lack of evidence to support the recommendation of one specific type of medication over another.
  - In the absence of definitive treatment recommendations, we must treat using the best available evidence.
  - It would appear that combined treatment with topical drugs that inhibit mast cells and block the effects of histamine (e.g., olopatadine) and drugs that reduce eosinophil activation (e.g., lodoxamide and spaglumic acid) and systemic antihistamines can be used as standard treatment for AKC and VKC.

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Antihistamines and Decongestants

- Mild allergic conjunctivitis can usually be managed with an over-the-counter antihistamine/decongestant or a topical 2nd-generation antihistamine
- Topical antihistamines provide short-term relief of eye itching and redness; they target histamine receptors, but do not target other pro-inflammatory mediators
- Long-term use of decongestants is associated with rebound congestion on discontinuation of therapy

American Academy of Ophthalmology. 2013;[1] O'Brien TP. *Curr Opin Allergy Clin Immunol.* 2013;13(5):543-549;[3] Bielory L, et al. *Allergy Asthma Proc.* 2013;34(5):408-420.[4]

Recommendations by the American Academy of ophthalmologist for the treatment of ocular surface allergy

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Antihistamines and Decongestants (cont)

- Remind patients to continue to follow allergen avoidance recommendations
- If symptoms persist or frequently recur, consider adding a mast cell stabilizer

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Mast Cell Stabilizers

- These agents do not relieve current symptoms, but are used to prevent mast cell degranulation with future exposure to allergens
- Reduction of mast cell degranulation prevents the release of histamine and other chemotactic factors
- If symptoms are not well controlled, consider adding a brief course (1-2 weeks) of a low-potency topical corticosteroid

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Topical Corticosteroids

- Effective against T-cell-mediated allergic conjunctivitis
- Consider when symptoms are not adequately controlled with antihistamine/vasodilator and mast cell stabilizer therapies
- Use lowest dose possible; slowly taper
- Educate patients that overuse of topical corticosteroids is associated with risk of increased intraocular pressures, glaucoma, cataract formation

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H1 receptor blocker and mast-cell stabilizer (dual action drugs)

- Olopatadine, epinastine, ketotifen and azelastine
- twice-daily dosing.
- they also exert anti-inflammatory effects
- olopatadine decreases the mucus discharge in VKC by reducing the goblet cell density in the conjunctiva

modified steroids

- loteprednol etabonate, rimexolone.
- have superior safety profile,
- highly effective in the acute and prophylactic treatment of allergic
- Fluorometholone is also a soft corticosteroid

Immunomodulators- Cyclosporine-A

- Topical CsA 1 or 2% emulsion in castor or olive oil
- In poor responders, or when only prolonged steroids are effective,
- CsA 1% was reported to be the minimum effective concentration in the treatment of vernal shield ulcer, with recurrence observed at lower concentrations.
- Lower concentrations of CsA (0.5%) have been suggested as a steroid-sparing agent with moderate-to-high effectiveness.
- No severe side effects of topical CsA, except for a burning sensation during administration, have been reported.

Immunossupressives-Mitomycin-C (MMC)

- Topical 0.01% MMC eye drops have been evaluated in patients with severe VKC refractive to the combination of mast cell stabilizers and steroid treatment and found to decrease ropy mucous discharge, photophobia, conjunctival hyperemia and limbal edema but not keratitis
- Giant papillae resection with intraoperative MMC 0.05% for 5 min has also been used in severe AKC and VKC patients with corneal complications, leading to a rapid resolution of clinical signs of ocular surface inflammation and corneal disease.
- Complications: eyelid skin erythema, irritation, discomfort, conjunctival and corneal inflammation, scarring, corneal epithelial defects, and corneal melting.

anti-VEGF drugs

- Topical avastin is a powerful inhibitor of corneal angiogenesis and lymphangiogenesis, and may prove to have a significant role in the prevention or management of inflammatory corneal neovascularization.
- Trials of topical anti-VEGF treatments for corneal vascularization are inconclusive.

Others in research

- Topical ocular anti-TNF-α drugs have been trialed in animal studies. There are no currently available topical formulations of anti-TNF-α drugs for human ocular use, but in theory TNF-α blockade could reduce inflammation without the toxicity of topical steroids.
- **Omalizumab** is a humanized monoclonal antibody against IgE used for the treatment of uncontrolled severe persistent allergic (IgE-mediated) asthma. It has shown some benefit in the management of acute allergic eye disease in combination with specific immunotherapy.
- **Rituximab** is an anti-CD20 agent that has proven to be effective in lymphoma and some autoimmune diseases, and may play a role in atopic dermatitis. it may prove to play a role in some CD4 cell-mediated disease such as severe allergic conjunctivitis.
- tacrolimus 0.02% ointment has been trialed on refractory ocular surface inflammatory diseases and showed a moderate-to-marked benefit, including suppression of corneal melting, remission of sclera-keratitis and reduction of giant papilla and corneal epithelial defect in severe AKC without obvious serious adverse events.

Allergen-specific Immunotherapy

- In general, the result of allergen-specific immunotherapy has been disappointing in the management of allergic eye disease.[
- Ongoing research into the balance between different T-cell subsets and especially regulatory T cells has reinvigorated the field of allergen-specific immunotherapy,[and it may be that improvements in vaccine design and administration will lead to more significant clinical results.
- The incidence of IgE-mediated reactions to allergen-specific immunotherapy continues to hamper clinical use

Systemic anti-histamines

- Oral anti-histamines are a good choice when allergy involves the eyes, nose or pharynx simultaneously.
- Topical anti-histamines provide faster and superior relief than systemic anti-histamines

MANAGEMENT SUMMARY

(Medscape Aug 19, 2011)

Surgical Treatment

Shield ulcers

- **Keratectomy for** corneal plaques is recommended to alleviate severe
- A combined treatment regime consisting of surgical removal of giant papillae and supratarsal corticosteroid injection followed by CsA (0.05%) and cromolyn sodium eye drops applied five-times daily has been proposed for the treatment of severe treatment-resistant shield ulcers.

Giant papillae excision

For mechanical pseudoptosis or coarse giant papillae

- combined with cryotherapy or MMC
- CO_2 laser

Amniotic membrane grafts /corneal epithelial transplant

- following keratectomy may help re-epithelization in deep ulcers.

Management of Vernal Keratoconjunctivitis- SUMMARY

- Various pharmacologic agents may be used to provide varying degrees of relief. Mucolytic agents, such as acetylcysteine, may help minimize the discharge and provide temporary relief. Vasoconstrictors may reduce hyperemia but are not effective in severe cases on a long-term basis. Similarly, topical antihistamines have no significant long-term benefit.
- Mast cell stabilizers are perhaps the mainstay of treatment of VKC and are safe for long-term use. However, topical corticosteroids generally become necessary for most patients with significant symptoms. Because of their potential adverse effects, topical steroids should be prescribed at the lowest effective concentration and for the shortest duration possible.
- A pulsed-therapy steroid regimen is generally recommended, such as 1% prednisolone acetate every 2 hours for the first week followed by a rapid taper; this may be repeated if symptoms recur. Systemic steroids may be used but generally are not necessary for moderate cases of VKC.
- Several reports have shown that topical cyclosporine (Restasis) may be effective in reducing some of the signs and symptoms of VKC without adverse effects. Oral aspirin has been shown to be effective. Treatment of corneal shield ulcer may require antibiotic-steroid ointments.

Management of Atopic Keratoconjunctivitis-summary

- Treatment of patients with AKC is similar to that of VKC, in that it includes controlling the environment and avoiding allergens and may require topical and systemic medications to provide symptomatic relief. As with VKC, topical vasoconstrictors and antihistamines may provide very limited, short-term relief; they are not the mainstay of treatment.
- As with VKC, topical mast cell stabilizers and topical corticosteroids provide significant relief of symptoms. Mast cell stabilizers have to be used for several weeks before taking effect; in the interim, topical steroids used in a pulsed fashion may help to control symptoms. Systemic antihistamines that are specific for H1 histamine receptors have been found to be helpful. Systemic steroids rarely are required, except in cases of vision-threatening complications.
- Systemic cyclosporine, which has been shown to be effective in the treatment of atopic dermatitis, has shown promise in controlling ocular inflammation in AKC. Postulated mechanism of action is inhibition of the ability of T lymphocytes to produce interleukin 2 (IL-2), which is responsible for recruiting and activating new T cells. However, as with any systemic therapy, adverse effects may be significant; therefore, monitoring of serum levels and renal function is essential.
- Concomitant herpes simplex virus infection should be treated with either topical or oral antiviral agents as needed. A subset of patients with recalcitrant and debilitating AKC may benefit from plasmapheresis, as was described by Aswad in 2 patients, one of whom had hyperimmunoglobulinemia E.

Management of Giant Papillary Conjunctivitis

- The goals of treatment in GPC are resolution of symptoms and restoration of functional use of contact lenses or ocular prosthetics. Although removal of the responsible foreign body is the definitive treatment, and that may be appropriate for exposed sutures or scleral buckles, complete discontinuation of contact lenses or ocular prosthetics may be met with some degree of resistance from patients. Fortunately, contact lens wear does not need to be completely discontinued to minimize the symptoms of GPC.
- Significant reduction in the signs and symptoms may be achieved by changing the contact lens care routine. Disinfecting solutions that contain chemical preservatives should be discontinued. Converting from soft daily-wear contact lenses to disposable or daily-disposable soft contact lenses may prevent the accumulation of proteinaceous deposits, which may be the antigenic stimulus for GPC.
- Rigid gas-permeable contact lenses may provide further relief from symptoms if disposable lenses do not provide adequate response. This relief is due to the decreased proclivity of the rigid gas-permeable contact lenses to develop adherent deposits and coatings.
- Pharmacologic treatment of GPC includes the use of mast cell stabilizers, topical corticosteroids, and antihistamines, as in VKC.