

Vernal Keratoconjunctivitis

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*There is no financial or proprietary
interest in a product, method, or
material described herein.*

ACD

- **Allergic conjunctival disease (ACD)** is defined as “a conjunctival inflammatory disease associated with a type I allergy accompanied by some subjective and objective symptoms.”
- Allergic conjunctival diseases in the entire population is estimated to be about **15-20%.**

Conjunctivitis: Schematic of Allergic Comorbidities

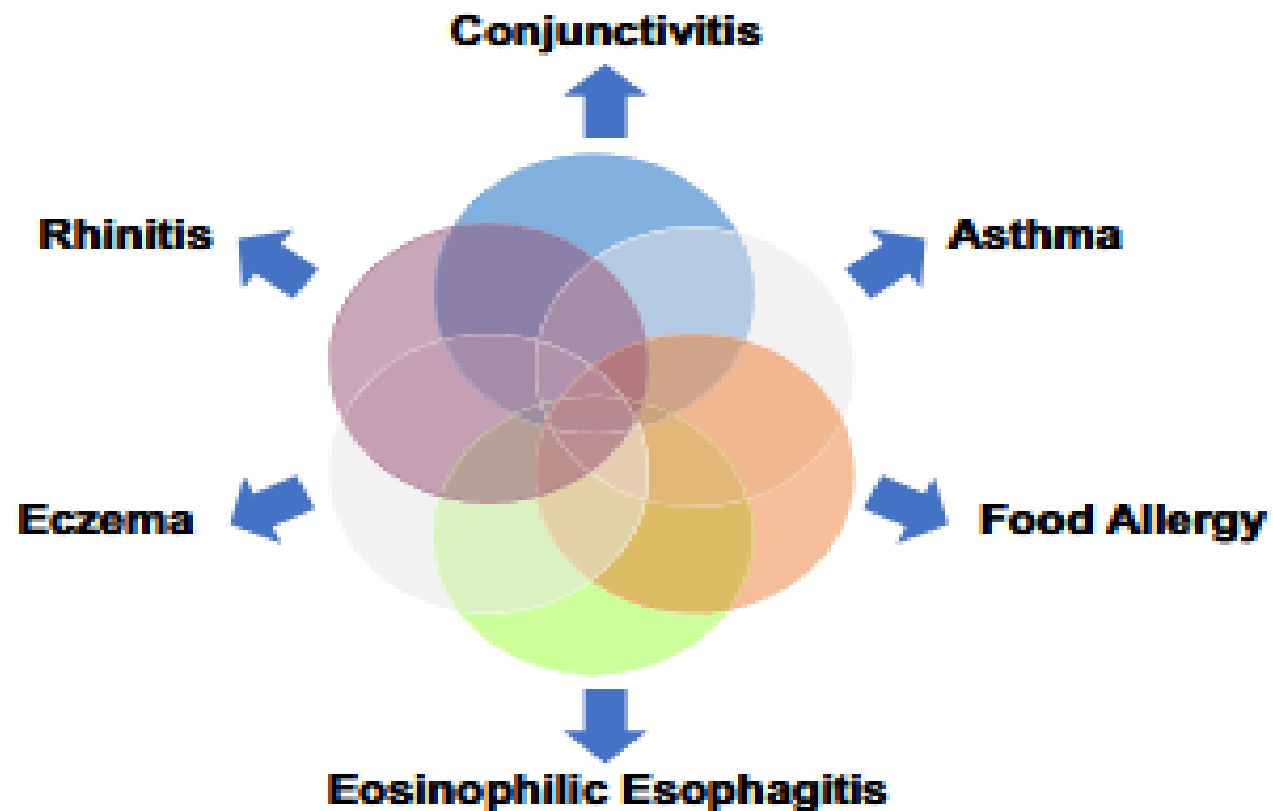
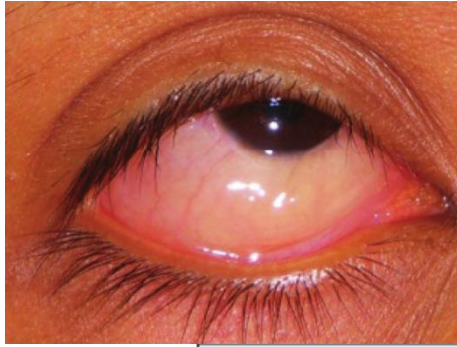


Fig. 1 Conjunctivitis: Schematic of allergic comorbidities [5, 6]

Allergic conjunctival diseases (ACD)

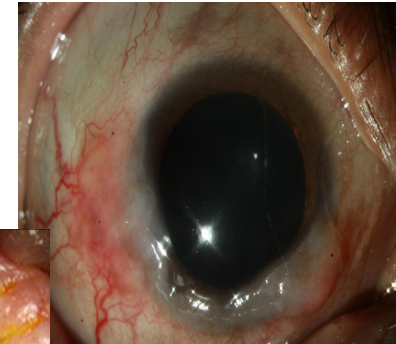
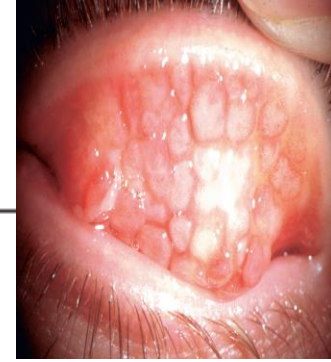


Allergic conjunctivitis (AC)

Atopic keratoconjunctivitis (AKC)

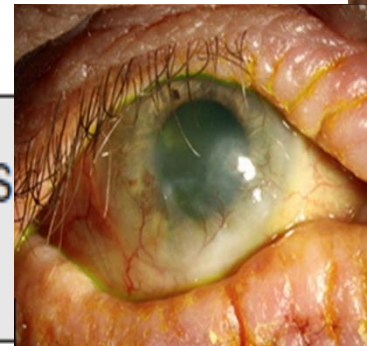
Vernal keratoconjunctivitis (VKC)

Giant papillary conjunctivitis (GPC)

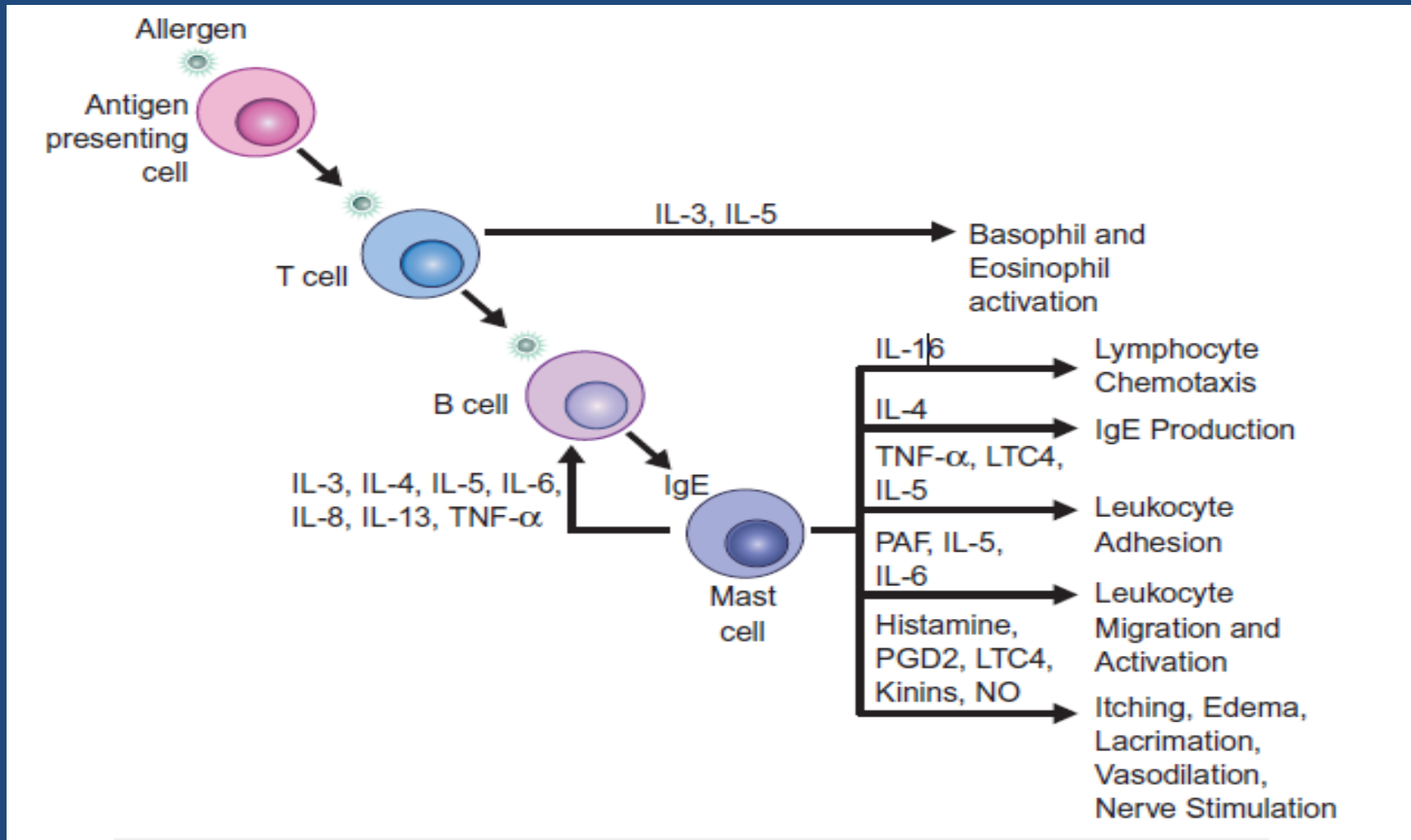


Seasonal allergic conjunctivitis (SAC)

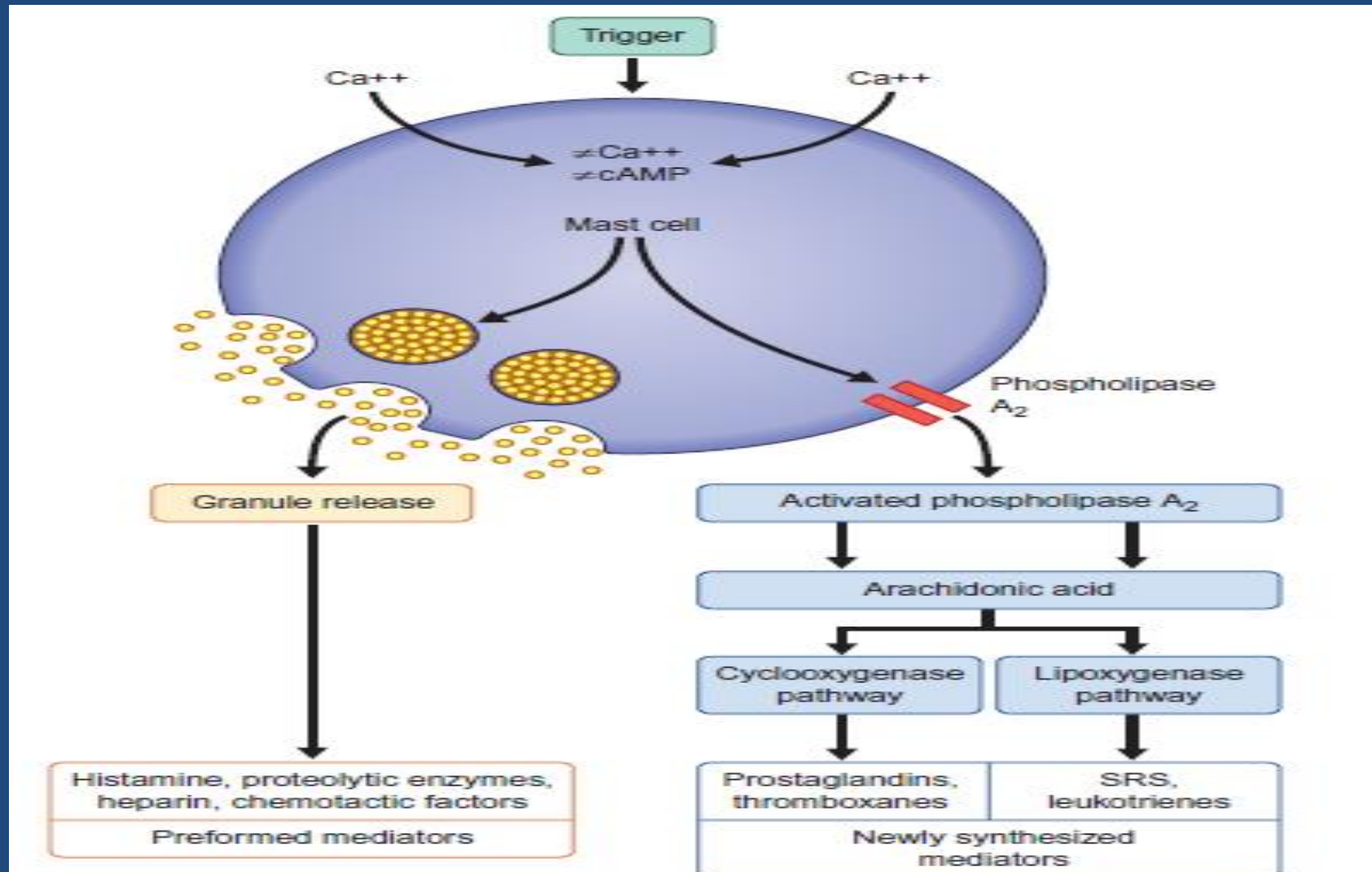
Perennial allergic conjunctivitis (PAC)



Mast Cell Activation Pathway



Mast Cell Activation Pathway



Definition of VKC

- **Vernal keratoconjunctivitis (VKC)** is a chronic, bilateral, conjunctival inflammatory condition found in individuals predisposed by their atopic background.
- The onset of disease is generally before age 10, it lasts 2 to 10 years, and it usually resolves during late puberty.



Epidemiology of VKC

Allergy : **30%** in US

Ocular Allergy : **15-20% in US**

VKC primarily affects children and teenagers, with a greater prevalence among boys than girls: the male-female ratio is at least **3:1**

Nebbioso M, Alisi L, Giovannetti F, Armentano M, Lambiase A. Eye drop emulsion containing 0.1% cyclosporin (1 mg/mL) for the treatment of severe vernal keratoconjunctivitis: an evidence-based review and place in therapy. *Clin Ophthalmol*. 2019;13:1147-1155. <https://doi.org/10.2147/OPTH.S181811> PMID:31308622

LSCD + VKC : 1.2%

- worsen in spring and summer

There is a significant history of other atopic manifestations, such as eczema or asthma in **40-75%** of patients with VKC.

A family history of atopy is found in **40-60%** of patients.

Vernal Keratoconjunctivitis

Pathogenesis:

- It is a seasonally, bilateral inflammation of the cornea and conjunctiva that occurs predominantly in **young males**, who frequently, have a personal or family history of atopy.
- The disease may persist year-round in tropical climates. The immunopathogenesis seems to involve both **types I and IV hypersensitivity reactions**.



Pathophysiology of VKC

- Biopsy of a tarsal conjunctival papilla :
Epithelium contains large numbers of mast cells and eosinophils.

Mast cells: neutral proteases tryptase and chymase.

Brush cytology : Eos. and PMNs/ Bas.

Specific IgE and IgG have been isolated from the tears of VKC patients.

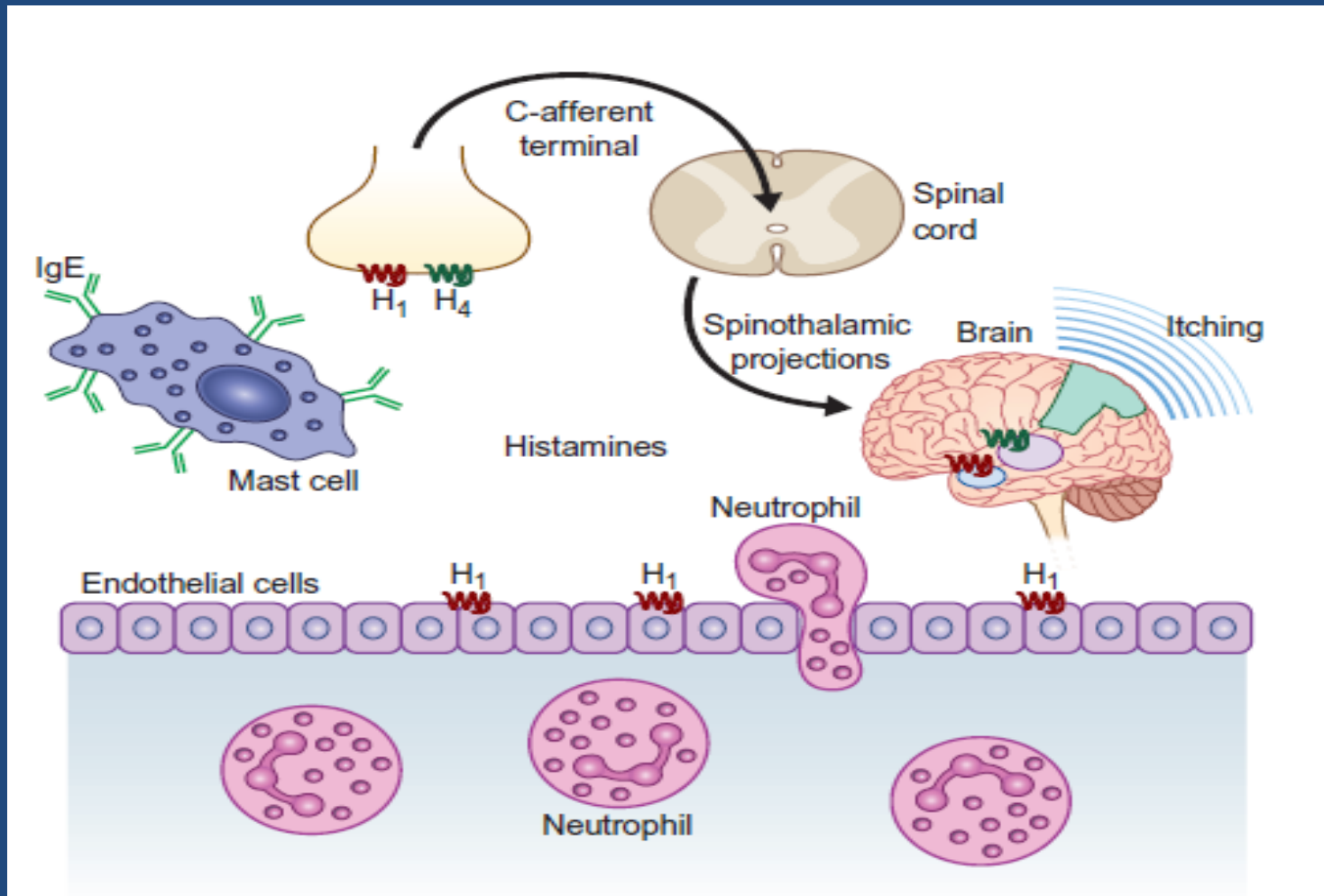
Pathophysiology of VKC

- Some neurotransmitters , their receptors, integrins, growth factors, Toll-like receptor 2, and the Inflammation modulating peptide thymosin-beta 4 are found in greater amount in VKC epithelium compared to normals.
- Eosinophil major basic protein and Eos. Cationic protein, Eos. Peroxidase, chollagenase
- **Substantia propria** : mast cells, basic fibroblast growth factor (bFGF)/ T-cell CD4+

Pathophysiology of VKC

- The substantia propria stains positive for metalloprotease 9, EGFR, VEGF, TGF-beta, bFGF, PDGF, and thymosin-beta 4 associated with inflammatory cells. Alpha-SMA-positive cells/collagen.
- Eosinophil major basic protein (EMBP) and cationic protein (ECP) are proinflammatory, and EMBP has been shown to be cytotoxic to corneal epithelium.
- *VKC is reported occur in patients with the hyperimmunoglobulin E syndrome.*

Pathophysiology of VKC



Symptoms of VKC

- ***Severe itching*** and ***photophobia*** are the main symptoms.
- Associated foreign body sensation, ocular hyperemia, ptosis, thick serous mucus discharge, and blepharospasm can occur.
- Intense photophobia and ocular pain are more specific for VKC.



Vernal Keratoconjunctivitis

Clinical presentation

- Symptoms consist of itching, blepharospasm, photophobia, blurred vision, and copious mucoid discharge. Clinically, 3 forms of VKC may be seen: *palpebral and limbal and mixed.*
- The palpebral VKC is predominantly a papillary reaction prominently in the upper region.



TABLE 1
Clinical Signs and Symptoms of VKC

	Notes
Symptom ^a	
Itching/chronic eye rubbing ^{6,18}	Characteristic of ocular allergy
Watering ^{6,18}	
Photophobia ^{6,18}	Suggestive of severe disease: urgent referral recommended
Pain/burning ⁶	
Redness ⁶	
Reduced vision ^{4,6}	Suggestive of severe disease: urgent referral recommended
Signs	
Tarsal papillae (cobblestones) ^{18,21}	
Limbal papillae ± Trantas dots ^{18,21}	Result from lymphocytic infiltration of the limbal conjunctiva ¹⁸
Punctate epithelial keratitis ⁶	
Conjunctival hyperemia ¹⁸	
Mucous discharge ⁶	Sign of active disease
Shield ulcer/clouded cornea ¹⁸	Suggestive of severe disease ¹⁸ : urgent referral recommended
Ptosis ⁹	
Coexisting atopic illness	
Association with asthma, eczema, other allergies (including food, medicine allergy) ⁶	

VKC = vernal keratoconjunctivitis

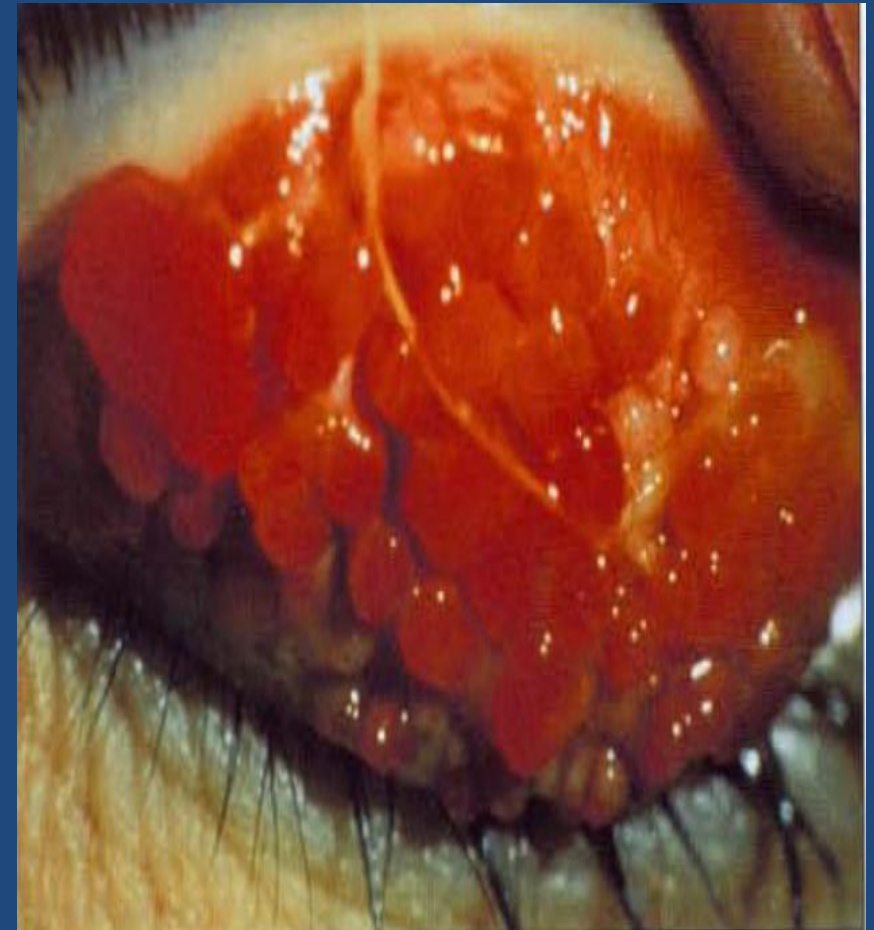
^aItching is a hallmark symptom of VKC; the defining signs are cobblestone papillae (subtarsal or limbal), with or without limbal follicles and/or Trantas dots.

Signs of VKC

- *Papillary response*

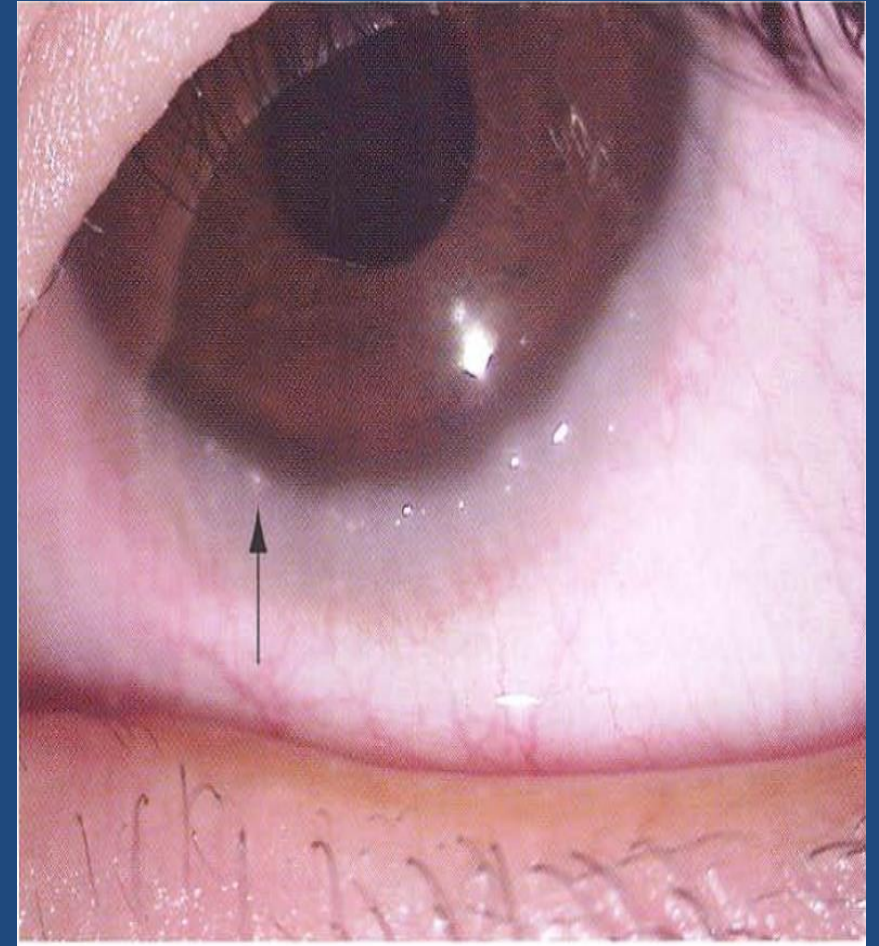
Conjunctival papillae is originated from epithelial proliferation in response to inflammation, in which the epithelium itself is hypertrophic.

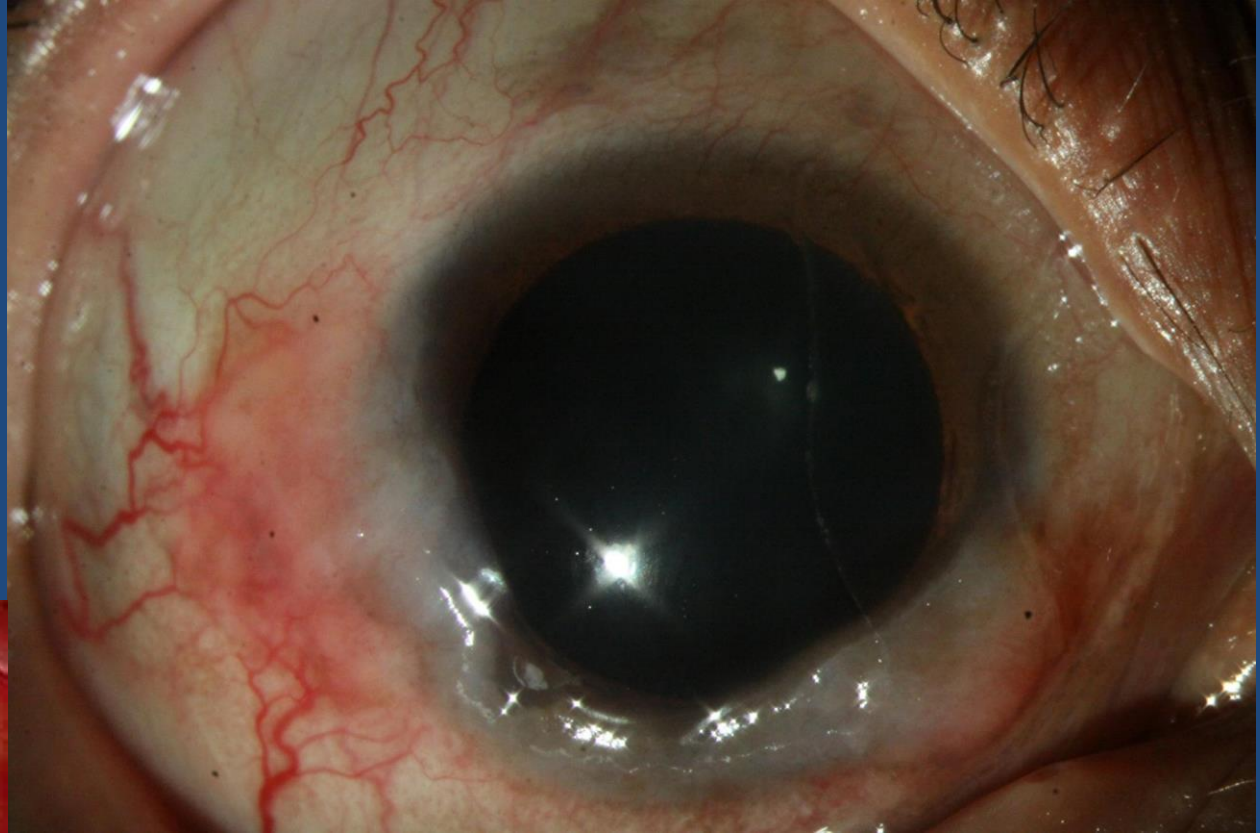
- **Giant papilla : > 1 mm**
- Fibrous prolif., lymph, mast cells, and Eos.

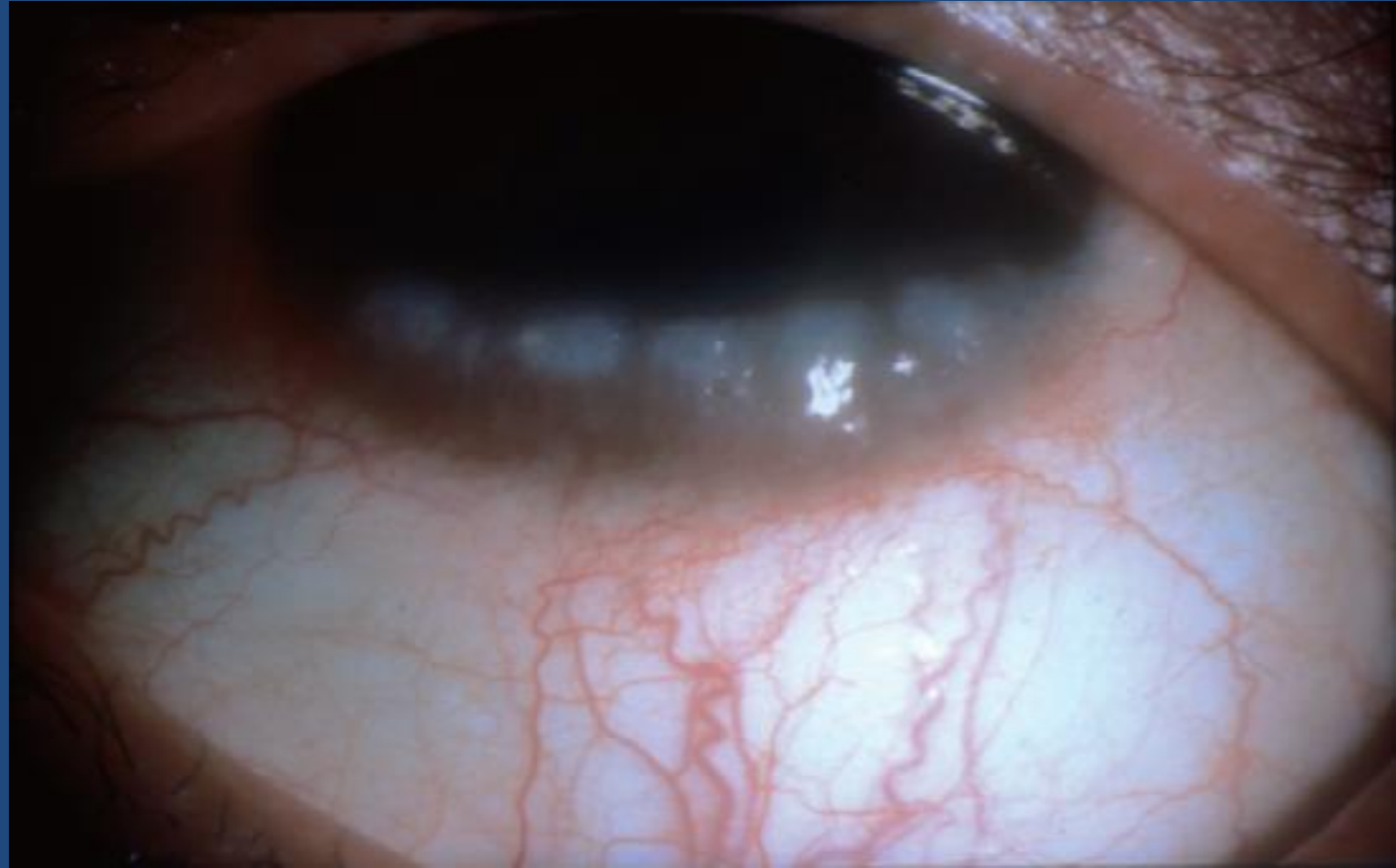


Limbal VKC

- Limbal papillae tend to be gelatinous and confluent, and they occur more commonly in African and west Indian patients.
- **Horner- Trantas dots**, which are collections of epithelial cells and eosinophils, may be found at *any meridian around the limbus*.
- These changes may lead to superficial corneal neovascularization.









Corneal signs

Inflammed tarsal conjunctiva → Release of mediators→

PEE → Frank epith. Erosion → IF no Tx or inadequate

Tx → mucus and fibrin deposition → impairment of epithelial

healing and NV → **Shield ulcer**

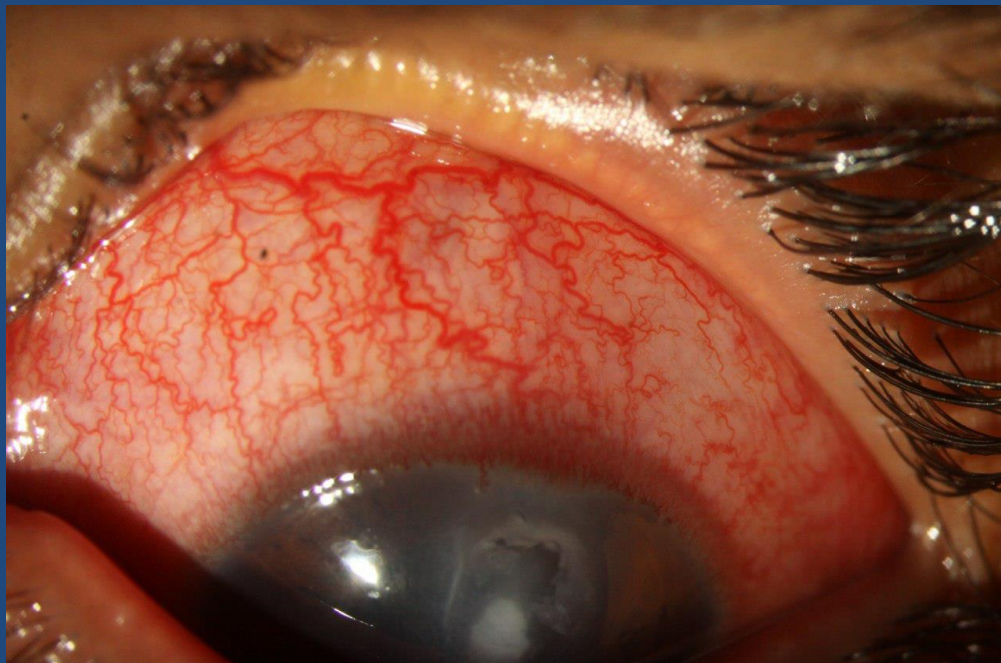


Vernal Keratoconjunctivitis

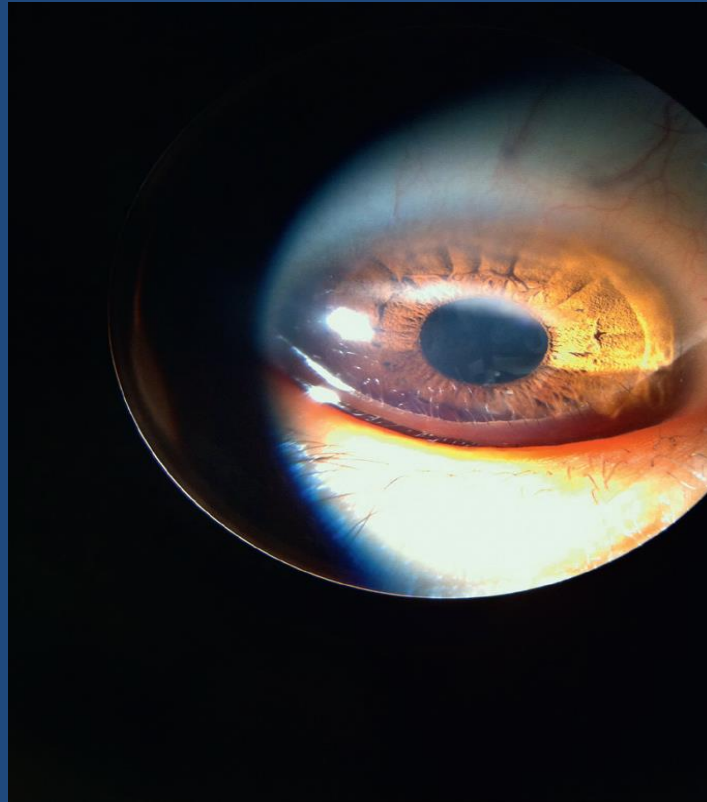
Clinical presentation

- Oval or shield-shaped noninfectious epithelial ulcers (the so-called shield ulcers) may develop.
- Opacification may develop in the central cornea .
- An association with atopy has been reported.
- Stem cell deficiency may also occur in severe cases.





Pseudogerontoxon



Bonini Clinical Grading Scale.²⁸

Grade	Symptoms*	Conjunctival hyperemia	Conjunctival secretion	Papillary reaction	Horner-Trantas dots	Corneal involvement
Grade 0 (quiescent)	Absent	Absent/mild	Absent	Mild to moderate	Absent	Absent
Grade 1 (mild intermittent)	Mild, occasional	Mild	Absent/mild	Mild to moderate	Absent	Absent
Grade 2						
2A (moderate intermittent)	Mild to moderate, intermittent	Mild	Mild	Mild to severe	Absent	Absent
2B (moderate persistent)	Mild to moderate, persistent	Mild to moderate	Mild to moderate	Mild to severe	Absent	Superficial punctate keratitis
Grade 3 (severe)	Moderate to severe, persistent	Moderate to severe	Moderate to severe	Moderate to severe with injection and swelling	Few	Superficial punctate keratitis
Grade 4 (very severe)	Severe, persistent	Moderate to severe	Severe	Moderate to severe with injection and swelling	Numerous	Corneal erosion or ulceration

Clinical Grading of VKC

VKC Grading	Symptoms	Conjunctival Hyperemia	Conjunctival Secretion	Papillary Reaction	Trantas Dots	Corneal Involvement
Grade 0 quiescent	None	None/mild	None	Mild to moderate	None	None
Grade 1 mild	Mild and occasional	Mild	None/mild	Mild to moderate	None	None
Grade 2A moderate	Moderate and intermittent	Mild	Mild	Mild to severe	None	None
Grade 2B moderate	Moderate and persistent	Mild to moderate	Mild to moderate	Mild to severe	None	Superficial punctate keratitis
Grade 3 severe	Moderate to Severe and persistent	Moderate to severe	Severe	Severe injection and edema	Few	Superficial punctate keratitis
Grade 4 critical	Severe and persistent	Moderate to severe	Severe	Severe injection and edema	Numerous	Corneal erosion or ulceration
Grade 5 evolution	None or mild	None or mild	None	Fibrosis and scarring	None	None

TABLE 2

Classification of VKC

VKC	Clinical Characteristic
Mild	–Treatment-naïve –No sight-threatening signs
Moderate	–Previously treated, with recurrence of symptoms OR –First presentation/treatment-naïve, with limbitis or larger tarsal conjunctival cobblestones, punctate keratopathy; mucous discharge
Severe	–Lack of response to prior treatments –Repeated flare-ups despite compliance with treatment –Presence of shield ulcer, significant corneal vascularization and/or disabling symptoms such as photophobia

VKC and Other Diseases

1. VKC + KCN : 26.8%, 28.9%

More hydrops

2. Fungal Keratitis

3. HSV Keratitis

VKC/AKC

- Patients with AKC frequently have disease year- round; seasonal exacerbation is minimal.
- Patients with AKC are older.
- The papillae are more apt to be small or medium-sized rather than giant.
- The papillae occur in the upper and lower palpebral conjunctiva.
- Milky conjunctival edema, with variable subepithelial fibrosis, is often present.

VKC/AKC

- Extensive corneal vascularization and opacification secondary to chronic epithelial disease (likely due to some degree of limbal stem cell dysfunction) can occur.
- Eosinophils seen in conjunctival cytology are less numerous and are less often degranulated.
- Conjunctival scarring often occurs and is sometimes so extensive as to produce symblepharon formation.
- Characteristic posterior subcapsular and/or multifaceted or shield-shaped anterior subcapsular lens opacities may occasionally develop.

VKC vs AKC

Table 49.1 Comparison of VKC and AKC

	VKC	AKC
Age	Younger	Older
Sex	Males > females	No predilection
Duration of disease	Limited; resolves at puberty	Chronic
Time of year	Spring	Perennial
Conjunctival involvement	Upper tarsus	Lower tarsus
Conjunctival cicatrization	Rare	Common
Cornea	Shield ulcer	Persistent epithelial defects
Corneal scar	Common; not vision threatening	Common; vision threatening
Corneal vascularization	Rare	Common

Prophylaxis : Self-Care

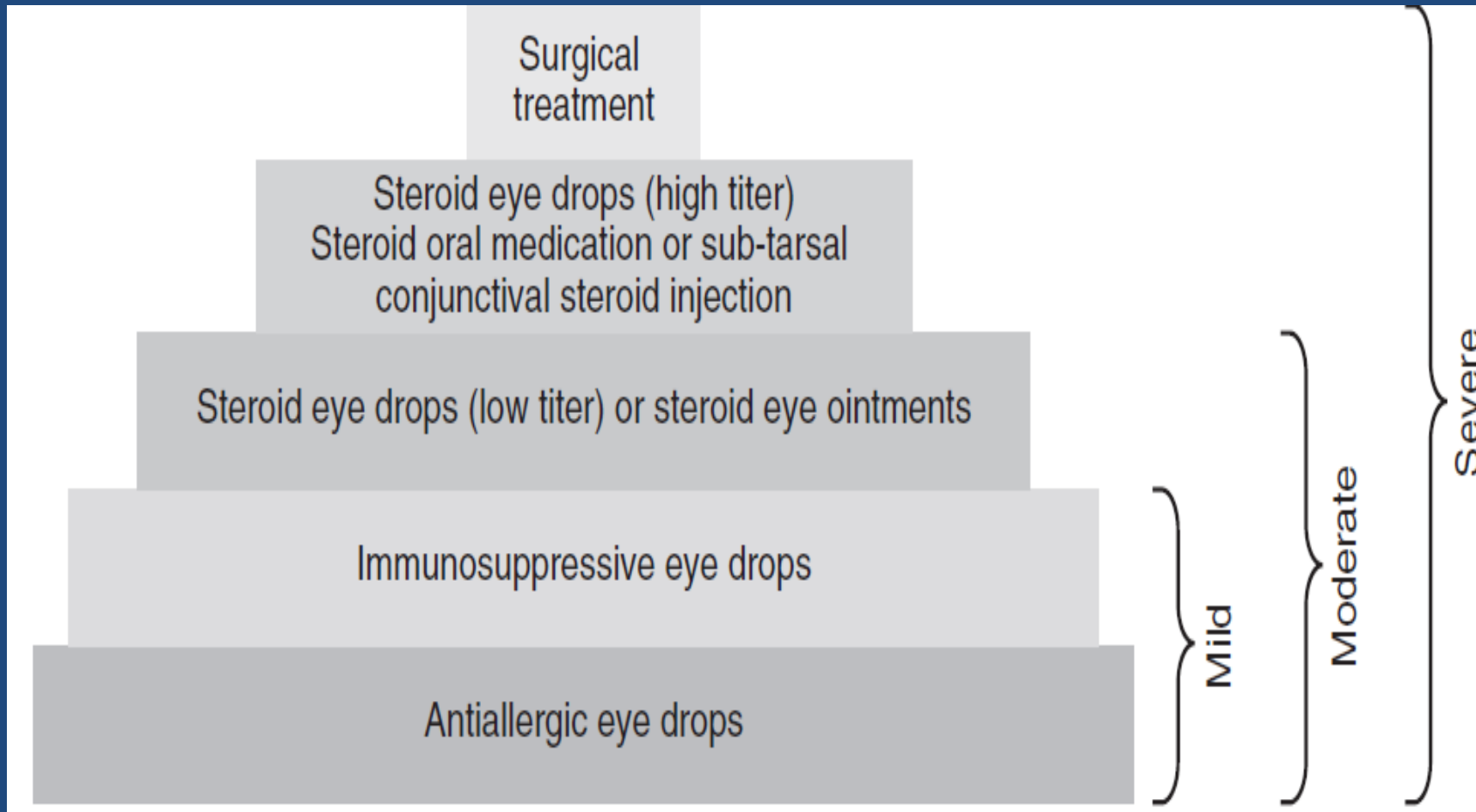
1. Avoidance and elimination methods by types of antigens.
2. Climatotherapy : Air-condition, Relocation
3. Self care for allergic conjunctivitis
 - Effect of Glasses for prevention of Pollens
 - Contact lens insertion
 - Eye Washing by Artificial tear
 - Avoidance of rubbing
 - Cold compresse
 - Alternate occlusion
4. Hyposensitization

Medical Treatment

- Vasoconstrictors
- Antihistamines
- Mast cell stabilizers
- Dual-acting agents
- NSAIDs
- Corticosteroids
- Immunosuppressive agents



Medical Treatment



	MILD DISEASE	MODERATE DISEASE	SEVERE DISEASE
Core therapy:	- Behavioral adaptation, education - Dual-acting agent (mast cell stabiliser, antihistamine e.g. ketotifen/olapatadine BD) - Cold compresses (Lubricants)	<i>As mild, plus:</i> - Short course of topical corticosteroids - Ciclosporin A 0.1% for long-term control (2–4x/day)	<i>As moderate, plus:</i> - Supratarsal steroid injection for shield ulcers/corneal involvement or if no response to topical steroids (4–6 wks) - Systemic ciclosporin for non-responders to treatment - Consideration: omalizumab for non-responders to ciclosporin (unlicensed)
Prescribed by:	- General practitioner - General ophthalmologist - Ophthalmologist in eye casualty	- General ophthalmologist (Ophthalmologist in eye casualty)	- Paediatric and/or corneal specialist - Multidisciplinary team
Optional additional therapy:	- Children are often already receiving oral antihistamine - Treatment for rhinitis/other atopic disorders as appropriate	- Tacrolimus to skin 0.03% BD in case of lid eczema (unlicensed for use in the eye) (PCR if concern about coexisting herpetic disease)	- Surgical therapy, e.g. corneal scrape - Oral steroids are an option where subtarsal injections are delayed
Next steps:	Discharge to primary care with comprehensive information	- Maintain treatment throughout spring and summer; try to wean off in autumn - Avoid long-term topical corticosteroids	- Regular fixed review - MDT management (incl. paediatric team) - Attempt to gradually reduce treatment once controlled
Management of ongoing care:	Primary care	General/pediatric ophthalmologist	Pediatric and/or corneal specialist

Figure 6. Summary of recommended management approaches for mild, moderate, and severe disease. PCR = polymerase chain reaction

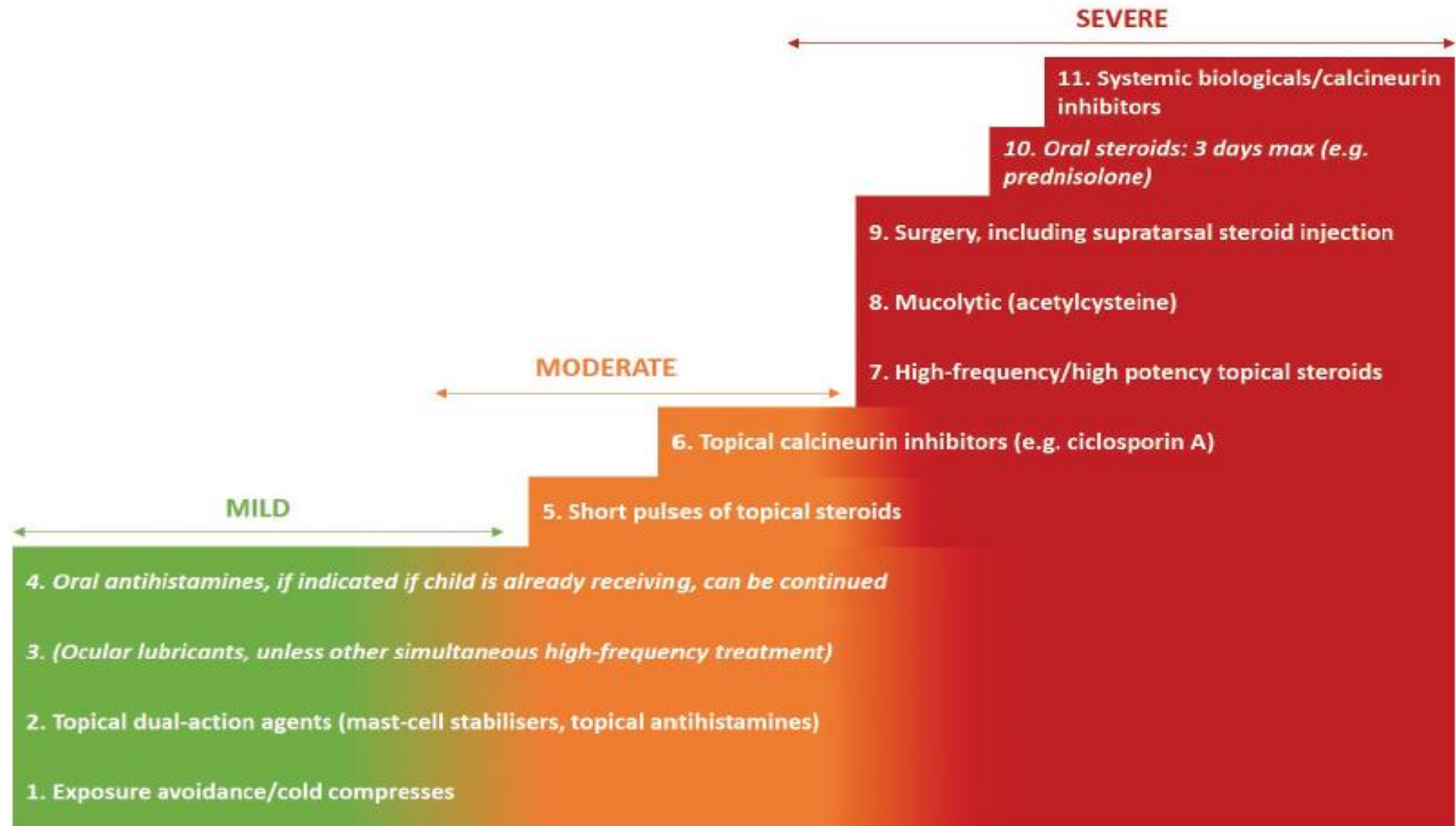


Figure 7. Treatment stepladder for vernal keratoconjunctivitis (VKC). Adapted from Leonardi A, Silva D, Perez Formigo D, et al. Management of ocular allergy. *Allergy*. 2019;74(9):1611-1630.

Decongestants (Vasocostrictors)

Ophthalmic Vasoconstrictors			
Vasoconstrictor	Duration of action (hr)	Available concentration	Prescription status
Naphazoline	3 to 4	0.012%,0.02%,0.03%,0.1%	otc Rx
Oxymetazoline	4 to 6	0.025%	otc
Phenylephrine	0.5 to 1.5	0.12% 2.5% 10%	otc Rx Rx
Tetrahydrozoline	1 to 4	0.05%	otc

ANTI HISTAMINE

- Levocabastine (Livostine) 0.05%
↓ ICAM-1
- Emedastine Difumarate (Emadine) 0.05%

Dosage : two drops per day

Mast Cell Stabilizer

- Cromolyn Na (Opticrom), 2%, 4%, qid
- Lodoxamide (Alomide) 0.1%, qid
- Neodocromil (Alocril) 2%, bid
- Pemirolast (Alamast) 0.1%, qid



Dual-action agents

- Epinastine 0.05% (Elestal; Allergan), bid
- Ketotifen 0.025% (Zaditor; Novartis), bid
- Azelastine 0.05% (Optivar; Medpointe), bid
- Olopatadine 0.1% (Patanol; Alcon), bid
- Olopatadine 0.2% (Pataday; Alcon), **daily**,

PH=7





It seems that all reported topical antihistamines and mast cell stabilisers reduce symptoms and signs of seasonal allergic conjunctivitis when compared with placebo in the short term.

However, there is no long-term data on their efficacy.

Direct comparisons of different antihistamines and mast cell stabilisers need to be interpreted with caution.

Overall, topical antihistamines and mast cell stabilisers appear to be safe and well tolerated. We observed a large variability in outcomes reported. Poor quality of reporting challenged the synthesis of evidence.

NSAIDs

- Ketorolac tromethamine (Acular) 0.5%, qid (FDA approval), inhibition of cyclo-oxygenase pathway.
- Diclofenac, Flurbiprofen, Nepafenac
- **Bromfenac 0.7% (Daily)**
- Discomfort in instillation
- Chronic use : Corneal toxicity
- **Does not relieve conjunctival hyperemia**



Corticosteroids

- Dexamethasone 0.1%
- Prednisolone phosphate 1% (**not prednisolone acetate**)
- 8 times /day for one week / every 2 hrs for 5-7 days
- Loteprednol Etabonate 0.5% (Alrex)
- Rimexolone 1%

Corticosteroids

- Systemic CSs only for :
 1. Severe VKC/AKC
 2. Bilateral Vision-threatening cases

Supratarsal Injection of CSs

1. Topical anesthesia
2. Cotton-tipped applicator soaked in 2% lidocaine on the upper tarsal border for one minute.
3. Inject 0.25 ml of 2% lidocaine+epinephrine (1:200,000) by a 26G needle
4. After 2 minutes, CS injection by 26G, 5/8 inch needle
5. ***Dexamethasone 2 mg, triamcinolone 40 mg, hydrocortisone 50 mg***

Immunosuppressive agents

- **Cyclosporine A 0.02-2%**
- Cyclosporin A (CsA) acts mainly on T cells by inhibiting calcineurin, which in turn controls the synthesis of many proteins involved in T-cell activation.
- It blocks the transcription and production of IL-2, thus limiting the activation of CD4+ and CD8+ T cells.
- In addition, CsA blocks the production of other lymphokines such as interferon- γ and inhibits the expression of high-affinity IL-2 receptors.



Tacrolimus (FK 506)

- Tacrolimus (Prograf) is a newer macrolide immunosuppressant produced by *Streptomyces tsukubaensis* with a mechanism of action very similar to CsA.
- It inhibits the activation T lymphocytes by interfering with calcineurin and therefore blocks the transcription of several lymphokines, most importantly IL-2.

- Topical tacrolimus with concentrations of 0.02–0.1% in ointment form has successfully been used for treatment of atopic keratoconjunctivitis (AKC), giant papillary conjunctivitis and VKC.



Topical 0.005% tacrolimus eye drop for refractory vernal keratoconjunctivitis

Abstract

Purpose To evaluate the efficacy and safety of topical 0.005% tacrolimus eye drop for treatment of refractory vernal keratoconjunctivitis (VKC).

Methods This prospective study included 20 eyes of 10 patients with refractory VKC, who had active symptomatic disease despite conventional medications including topical steroids. After discontinuing all other medications, patients were treated with topical 0.005% tacrolimus eye drop four times a day. Changes in subjective symptoms and objective signs after treatment were evaluated, and development of possible complications was assessed.

Results Mean age of patients was 21.3 ± 7.4 years and mean duration of VKC was 12.1 ± 5.8 years. After starting tacrolimus eye drop, patients were followed for a mean duration of 10.7 ± 3.7 months (range, 6–15 months). All symptoms including itching, redness, photosensitivity, foreign body sensation, and mucus discharge improved after the treatment; itching was the first symptom to show dramatic relief. In addition, there was improvement in objective signs including conjunctival hyperaemia, conjunctival papillary hypertrophy, giant papillae, limbal hypertrophy, corneal punctate epithelial erosions, and corneal pannus; conjunctival hyperaemia was the first sign to show improvement. No patient required addition of other medications including steroids for further relief. Any attempt to discontinue tacrolimus eye drop was associated with recurrence of patients' symptoms and signs, necessitating continued use of the medication during the entire follow-up time. No ocular complication related to tacrolimus was noted.

Conclusion Topical 0.005% tacrolimus eye drop seemed to be a safe and effective treatment for steroid-resistant refractory VKC;

A Kheirkhah¹, MK Zavareh¹, F Farzbod¹, M Mahbod² and MJ Behrouz¹

however, long-term use was needed to control the disease.

Eye (2011) **25**, 872–880; doi:10.1038/eye.2011.75; published online 8 April 2011

Keywords: allergy; giant papillae; tacrolimus; vernal keratoconjunctivitis

Introduction

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, seasonally exacerbated, allergic inflammation of the ocular surface, involving tarsal and/or bulbar conjunctiva. It is more common in children and young adults who have an atopic background. Although VKC has traditionally been considered as a classical IgE-mediated disease (type I hypersensitivity), recent findings implicate more complex pathogenesis with particular involvement of Th2 lymphocytes.¹

For treatment of VKC, a variety of medications have been used which include anti-histamines, mast-cell stabilisers, and non-steroidal anti-inflammatory drugs. Nevertheless, topical steroids are the mainstay of treatment for moderate–severe forms of VKC.^{2,3} Some cases, however, remain still symptomatic despite treatment with topical steroids. Furthermore, prolonged use of topical steroids may be associated with various complications, such as glaucoma, cataract, and secondary infections.² To avoid steroid-related complications, immunomodulatory agents such as topical cyclosporine A have recently been used for treatment of VKC.^{4–6}

Tacrolimus (formerly, FK-506) is another immunomodulatory agent, which is similar to cyclosporine A in mechanism but with much higher potency (up to 100 times).⁷ It suppresses T-cell activation, T helper cell-mediated B-cell proliferation, and formation of cytokines, especially interleukin-2. In ophthalmology,

A photograph of a misty forest path. The path is a narrow, winding trail of dark brown earth, partially covered with green moss and small plants. It leads from the foreground into the distance, where it disappears into a thick mist. On the left side of the path, there are large, dark tree trunks and dense green foliage. On the right side, there is a thick wall of green ferns and other forest plants. The overall atmosphere is serene and mysterious.

THANK YOU FOR YOUR
ATTENTION