

OCULAR ALLERGY

Shirani Naidoo

Emergency and Ambulatory Paediatrics, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town

Email | shirani.naidoo@uct.ac.za

ABSTRACT

Ocular allergy is an umbrella term that encompasses several clinical phenotypes, each with its own individual presentation, clinical findings and outcomes and treatment. The majority of patients will have seasonal or perennial allergic conjunctivitis which are IgE-mediated conditions with defined triggers. The more severe forms of ocular allergy have both IgE and non-IgE mechanisms and a more severe clinical course. Treatment must be titrated against the type and severity of the disease, but patients with all forms of ocular allergy can expect good outcomes when it is adequately assessed and correctly managed in a multi-disciplinary team.

OCULAR ALLERGY

Ocular symptoms are among the most frequent symptoms experienced by atopic patients. The vast majority of these patients will have allergic rhino-conjunctivitis, where redness and itch are the most common symptoms.¹

Ocular allergy (OA) encompasses a wide range of conditions from seasonal allergic conjunctivitis (SAC), with short-lived redness and itch, to conditions such as atopic keratoconjunctivitis (AKC), where corneal damage and visual impairment can occur. Clinical needs can sometimes be met by simple over-the-counter medication, but some patients may require a multi-disciplinary team, including an allergist and an ophthalmologist, to help them control their symptoms.

The adverse effects of OA flow cumulatively from symptoms of the actual condition, medication effects and downstream clinical complications. The economic burden comprises direct treatment costs and time lost from productive work and study. In low- and middle-income countries (LMIC) particularly, under-resourced health systems have little to spare for a condition thought to be so innocuous. Accordingly, many patients will have their symptoms dismissed by a healthcare provider, with a consequent negative effect on their quality of life (QoL) and socio-economic prospects.^{1,2}

This article aims to provide an overview of OA and focuses on the clinical presentation, classification, diagnostics and treatment.

The eye is simultaneously isolated from adjacent organs and the systemic immune system and exposed to a host of allergens and irritants from the external environment. OA can involve the entire ocular surface including conjunctiva, eyelids, cornea, lacrimal glands and tear film. A complete review of the immunology of OA is beyond the scope of this article, but articles by Amod et al and Mashige, among others, can be referred to for more detail.^{3,4,5}

The prevalence of allergic conjunctivitis is increasing, particularly in developing countries with increasing affluence, rapid urbanisation and/or increasing air pollution, notably in Latin America, Asia and West Africa.^{6,7} Tunisia and Nigeria were among the top three sites for average prevalence rates of rhino-conjunctivitis in children between 13 to 14 years in Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC).⁸ A potential confounder of these prevalence studies is that the majority of studies do not differentiate between rhino-conjunctivitis and OA, merely documenting ocular symptoms.^{1,8,9}

OCULAR ALLERGY IN AFRICA

OA in Africa faces many challenges. Low levels of awareness of OA and low rates of health-seeking for eye symptoms have been noted in repeated studies, even among cohorts with higher socio-economic status and education levels.^{10,11,12} Ocular symptoms increased with the advent of the HIV era, due to both infectious and inflammatory conditions. HIV should be considered if an adult patient, with no previous history of OA presents with new-onset allergic conjunctivitis, in a high-prevalence area.¹³

The role of atopy in OA in Africa is a contentious issue. A large body of literature has examined the link between vernal keratoconjunctivitis (VKC) and atopy, which proposes that African children with VKC do not have co-morbid atopic disease – in sharp contrast to international experience. Generally, these studies focused on detailed ocular evaluation, with a questionnaire-based evaluation of asthma or rhinitis and without any objective assessment of sensitisation.^{10,14,15,16} South African studies in the field of asthma, rhinitis, food allergy and eczema have mirrored international trends.^{17,18,19} This relationship between atopy and OA in Africa therefore represents an important research gap, which is beginning to be explored – for example, a tertiary cohort from Egypt recently reported high rates of indoor aeroallergen sensitisation in patients with isolated allergic conjunctivitis.²⁰

TABLE I: CLINICAL FEATURES OF THE MAJOR OCULAR-ALLERGY SYNDROMES, INCLUDING THE UNDERLYING HYPERSENSITIVITY MECHANISM AND OPHTHALMOLOGICAL PRESENTATION^{1,2}

	SEASONAL AC	PERENNIAL AC	VKC	AKC	GPC	CBC
Presentation	Intermittent	Persistent	Persistent ± acute exacerbations	Chronic	Persistent	Chronic ± acute exacerbations
Mechanism	IgE mediated	IgE mediated	IgE & non-IgE mediated	IgE & non-IgE mediated	Non-allergic	Non-IgE mediated
Background	Atopic	Atopic	Childhood ± atopic	Adult atopic	Atopic or non-atopic	Non-atopic
Eyelids	Oedema	± Oedema	Oedema pseudoptosis	Eczema + meibomitis blepharitis		Erythema, eczema
Conjunctiva	Follicles ± papillae	Follicles ± papillae	Giant papillae	Papillae ± fibrosis	Giant papillae	±Hyperemia Follicles
Limbus	Nil	Nil	Trantas dots ±Thickened	±Thickened	Hyperaemia	Nil
Cornea	Nil	Nil	SPK ±Ulcer ±Vernal plaque	SPK Ulcer, plaque, opacities, neovascularisation	Rare	Nil

VKC – vernal kerato-conjunctivitis; AKC – atopic kerato-conjunctivitis; GPC – giant papillary conjunctivitis; CBC – contact blepharo-conjunctivitis; SPK – superficial punctate keratitis

CLASSIFICATION

Historically, several tools have been used to classify OA. These include:

- visual inspection and clinical characteristics (see Table I);
- using the underlying pathophysiology (see Table I);
- using the Gell and Coombs hypersensitivity mechanisms.

Uniform nomenclature for all atopic diseases, irrespective of target organ, was proposed by the European Academy of Allergy and Clinical Immunology (EAACI) in 2001 and validated by the Nomenclature Review Committee of the World Allergy Organisation (WAO). This places the highest emphasis on the *identification of the immunological mechanism(s)*, and stratifies ocular symptoms as *Ocular allergy (IgE or Non-IgE)* or *Ocular hypersensitivity* (predominantly irritative) (see Figure 1).¹ Symptoms should be considered as *intermittent or persistent, and mild, moderate or severe* according to their evolution and severity (similar to the ARIA guidelines).²¹

NB: The more severe forms of OA may have a condition-specific grading system or they may have purely eye complications, and do not always fit neatly into this system.^{1,22}

CLINICAL PRESENTATION

The anatomy and physiology of the nasal mucosa and conjunctiva are similar and rhino-conjunctivitis is the commonest cause of eye symptoms.⁴ There is a wide differential diagnosis for eye symptoms beyond allergy and atopic disease (see Text Box 1 for the red flags for a non-allergy condition).²³

TEXT BOX 1: RED FLAGS FOR A NON-ALLERGIC CONDITION²²

- Unilateral disease
- Foreign-body sensation
- Pain
- Purulent discharge
- Lid-margin disease
- Elderly onset

AGE OF ONSET

SAC and PAC usually present during adolescence and young adulthood (80% of patients are younger than 30 years old) and infrequently in older patients. VKC is generally a condition of prepubertal boys, whereas AKC symptoms often appear between 30 and 50 years of age.¹

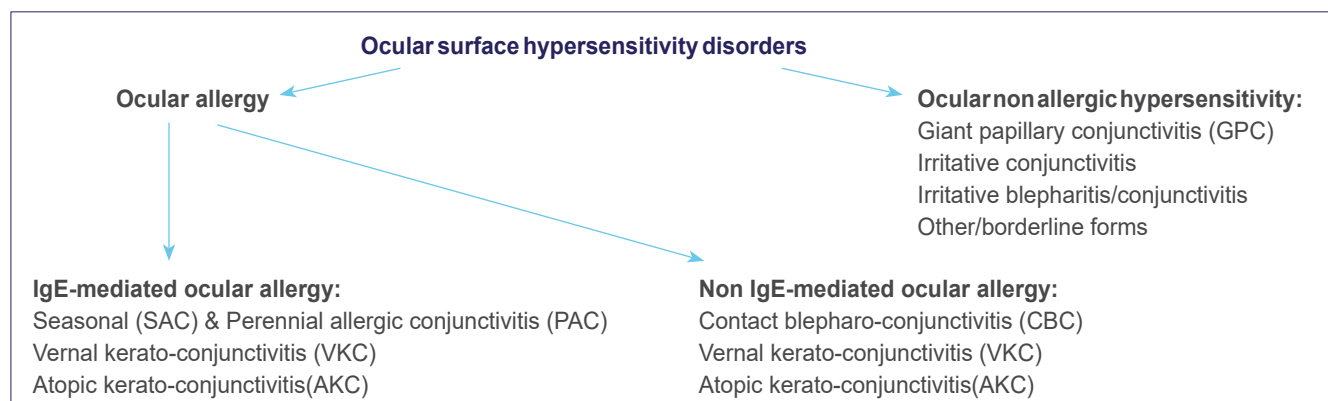


Figure 1¹

TYPICAL FEATURES OF OA

These include:^{12,23}

- Conjunctival injection (mild to severe)
- Conjunctival oedema (chemosis) (mild to severe)
- Itching
- Clear discharge (mild)
- Trantas dots (vernal or atopic)
- Corneal plaques (vernal or atopic)
- Cataracts (atopic).

CLINICAL COMPLICATIONS OF SEVERE OA

These include:

- Corneal epithelial erosions, shield ulcers and plaques can occur in both AKC and VKC.
- Keratoconus – a progressive, non-inflammatory disorder of the cornea, with thinning and distortion of corneal shape that causes irregular astigmatism and a subsequent decrease in visual acuity (VKC and AKC).^{13,14,24,25}

SEASONAL ALLERGIC CONJUNCTIVITIS (SAC) OR PERENNIAL ALLERGIC CONJUNCTIVITIS (PAC)

The mechanisms of SAC or PAC are via IgE-mediated reactions, with sensitised mast cells releasing a short burst of pre-made mediators, particularly histamine, tryptase and prostaglandins. This acute phase can be followed by a late phase resulting from the effect of mast-cell mediators on vascular epithelium.

A trigger or specific IgE antibodies to seasonal or perennial allergens can often be elicited on history or investigations. SAC is the disease of spring and summer caused by airborne pollens; PAC can be related to dust mites, animal dander and moulds with year-round symptoms. Conjunctival injection, chemosis and itching are the most common clinical features of SAC and PAC.^{1,5}

VERNAL KERATO-CONJUNCTIVITIS

VKC has a very strong association with prepubertal boys living in warm/

tropical regions. It is the most important form of OA in Africa and has been extensively studied. Regional VKC prevalence studies in children have yielded rates of up to 4 per cent (population-based study in Rwanda)¹² and 5% (Chad and Djibouti).¹⁰ The predominant symptom is intense ocular itching and tearing with a stringy mucoid discharge and severe photophobia. This is a more severe form of OA with a complex immunology that includes IgE and non-IgE mechanisms.^{1,24,26}

There are three clinical types:

- palpebral VKC with papillary hyperplasia of the upper tarsal conjunctiva;



Figure 3: Cobblestone papillae on the superior tarsal plate (palpebral VKC) (Curr Allergy Clin Immunol 2006;19(2):61)

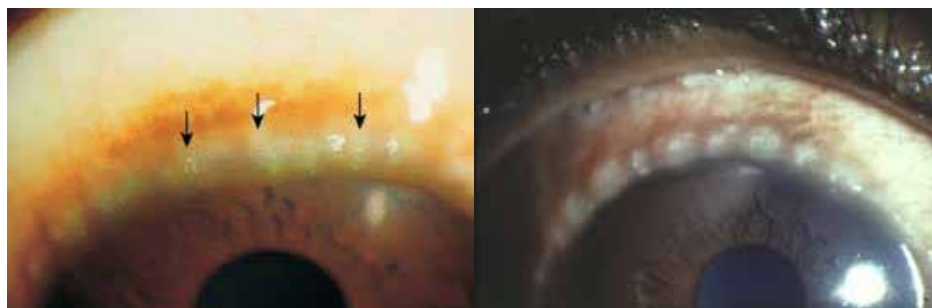


Figure 4: Limbal VKC – Papillae at the limbus (black arrows) are seen as gelatinous translucent nodules. Trantas dots are seen as small white concretions.) (Curr Allergy Clin Immunol 2006;19(2):62)



Figure 2: Seasonal and perennial allergic conjunctivitis: mild chemosis and hyperaemia of the palpebral and bulbar conjunctiva (Curr Allergy Clin Immunol 2015;28(4):276)

- limbal VKC with nodules in the limbal subconjunctival tissue and Horner–Trantas dots;
- mixed VKC.

The clinical picture is highly preserved, with palpebral forms more prevalent in Europe and the Americas. Mixed and limbal forms are more commonly seen in Asia and Africa.¹⁵ The seasonal peak is also not as prominent in the African cohorts.²⁶

ATOPIC KERATO-CONJUNCTIVITIS

AKC is a less common but more severe form of OA. It is strongly associated with atopy – atopic dermatitis, high-serum IgE and polysensitisation.^{1,14} The clinical picture includes the involvement of the eyelids, which often thicken and indurate, and can fissure. Conjunctival redness and chemosis are seen predominantly in the inferior fornix and palpebral conjunctiva. Similarly to VKC, the limbus and the cornea can be involved. AKC may be associated with *Staphylococcus aureus* colonisation of the eyelid and/or Meibomian gland dysfunction.^{1,12}

CONTACT BLEPHARO-CONJUNCTIVITIS (CBC)

CBC is also a mixed IgE and non-IgE condition. The predominant symptoms are itching and burning of the eyelid, but they can include oedema, eyelid skin redness, eczema or lichenification, conjunctival redness and papillae. Likely triggers include substances applied into or around the eye (medications, cosmetics, etc) and there is a lag between exposure to the allergen and the occurrence of symptoms.^{1,12,23}

INVESTIGATION

The investigative pathway for OA has predominantly been history-taking and examination, with a few targeted investigations.

History includes:

- detailed eye symptoms;
- symptoms of potential co-morbid atopic diseases;
- any other systemic conditions that can mimic OA (consider autoimmune conditions or immune-compromise),

The effect of eye symptoms on the activities of daily living and QoL is vital for a complete assessment. A number of QoL scores have been used in atopic disease: these include the Juniper score and its derivatives and a tool developed and validated specifically for VKC by Sachetti et al.^{17,27}

Examination should always include a detailed examination of

- the conjunctiva, cornea and eyelids (including tarsal surface);
- evidence of atopic disease;
- systemic conditions.

Slit-lamp examination is sometimes required and intraocular pressure monitoring is indicated if topical steroids are being prescribed. Visual-acuity assessment will be required only if there has been corneal damage or keratoconus (VKC and AKC).

If there are no red flags on history-taking or examination that suggest a non-atopic cause for the eye symptoms, then investigations may be confined to looking for evidence of an IgE-mediated allergy.

Skin-prick testing (SPT) is the gold standard for evaluating specific IgE responses in routine clinical practice, but any testing modality from serum IgE to component testing can be used. The in-vitro testing modalities are particularly useful if one suspects that a positive result represents a cross-reaction rather than from true sensitisation.^{1,12,23,28}

A number of new techniques are being evaluated in research settings which may migrate to clinical practice in the future. Tear-film assays (for trace levels of specific IgE or cytokine assays) are used to refine the immune footprint of each individual type of OA. Tear fluid is easily harvested from the affected organ and holds the potential of identifying biomarkers that may predict more severe disease outcomes or disease resolution or relapse in the case of the severe forms of OA.^{18,19,29,30}

Conjunctival ocular-challenge tests are the equivalents of open-food challenges, they are used in cases when an allergic trigger is strongly suspected but not proved on SPT or other immunological tests. They are similarly 'expensive' in terms of time and resources. Standardised allergens are available and systemic side-effects are rare.^{1,12,23}

TEXT BOX 2

The range of conditions encompassed by OA is notable.

Rhino-conjunctivitis while common, has a less severe symptom profile, whereas the severe forms of OA can be devastating.

Treatment regimens must be titrated against the specific type and severity of OA. The need for more potent treatment agents must be measured against potential complications (both short-term and long-term) and cost. This is particularly important in the case of the use of immunomodulators and biological agents.

TREATMENT

General principles apply in the treatment of OA. The lowest dose and potency of medication should be used, avoiding polypharmacy, where possible, and cumulative disease and medication side-effects are to be anticipated and avoided, if possible.

A treatment schedule must also be compatible with a patient's lifestyle – for example, multiple daily applications of topical medication are challenging for a working adult and almost impossible to achieve in a school-going child.²

The impact of resources and access to care cannot be underestimated, particularly in the more severe forms of OA.^{20,31} VKC cohort studies in the same year by Caputo et al from Italy reported excellent outcomes with minimal corneal issues,^{21,32} whereas ocular complications were seen in around 30% of patients with 6% of keratoconus in Kashmir by Sofi et al.^{22,33}

NON-PHARMACOLOGICAL OPTIONS

Non-pharmacological options are often underutilised. These include:

- Avoiding environmental triggers – light/dust/saltwater (sunglasses, goggles for swimming etc).
- Using saline drops or artificial tears to overcome dryness and provide a barrier for allergens and particles and dilute inflammatory mediators.
- Applying cold compresses, which act as vasoconstrictors and soothe both chemosis and itch.
- Avoiding allergic triggers, if present.

PHARMACOLOGICAL OPTIONS

Topical alpha-adrenergic agonists (vasoconstrictors)^{1,2}

- They are frequently used as first-line treatment because of their easy availability.
- They alleviate hyperaemia only and should be used short-term only.
- The side-effects include rebound redness, chronic follicular conjunctivitis and tachyphylaxis.

Topical antihistamines, mast-cell stabilisers and dual-acting agents¹

- Topical antihistamines and mast-cell stabilisers are safe and well tolerated; however, dual-acting agents provide better symptom control.
- There are good data regarding the use of dual agents in SAC/PAC and VKC, whereas the evidence base for AKC is less robust.²
- The side-effects include a local burning, stinging sensation, blurred vision and unacceptable aftertaste.

Non-steroidal anti-inflammatory drugs NSAID (topical prostaglandin and oral leukotriene inhibitors)

- Local side-effects of NSAIDs (burning/stinging after application) limit usage.
- Oral leukotriene inhibitors have a role to play in treating ocular symptoms in SAC and PAC, but are less effective than oral antihistamines in adults.²

Topical corticosteroids (CS)

- These are clinically effective and cost-effective anti-inflammatory agents.^{4,15,20,26,31}
- The side-effects include increased intraocular pressure and the potential for glaucoma, cataract formation and the risk of secondary infections;^{1,2} the lowest potency for the shortest period is therefore advised or, alternatively, pulsed therapy for flares.²
- Co-management by an ophthalmologist is required when using topical CS.

NB: Topical CS creams are sometimes required for AKC for severe acute eyelid eczema, and supra-tarsal injections are rarely used for highly treatment-resistant VKC and AKC.^{15,26}

Topical calcineurin inhibitors

- Topical cyclosporine is a steroid-sparing agent in severe VKC and AKC, with data available to support their safety and efficacy.
- Tacrolimus is also being used, though with a less robust database.^{1,2}

Systemic antihistamines

- They are frequently used for co-morbid allergic disease such as allergic rhinitis (AR).
- They are highly effective in the treatment of allergic rhinoconjunctivitis, but their effect on true OA is hard to assess as most studies have looked at total symptoms without evaluating their impact on eye symptoms alone.

NB: Mucosal dryness is a risk, which may exacerbate OA of any kind and sedation with first-generation agents.^{1,2}

Biologicals

- Omalizumab (anti-IgE antibody) has been used in refractory VKC and AKC, and there is an increasing body of evidence regarding this agent.^{23,24,25,34,35,36}

Allergen-specific immunotherapy (AIT)

- AIT can be considered in moderate-to-severe ARC that has not responded to normal therapy and/or avoidance strategies if there is evidence of IgE sensitisation.
- AIT may be considered for isolated SAC and PAC, although the evidence base is less robust.^{1,2}
- The evidence base for AIT in VKC and AKC is minimal,^{23,37} and patients would have to be managed individually.

CONCLUSION

OA encompasses a range of clinical entities across all age groups, with a small number of severe subsets. Eye symptoms can be a window into a systemic medical condition or one of the manifestations of allergic disease in an atopic individual or isolated OA. Research gaps exist and collaborative work is needed to understand the full impact of OA in Africa. Overall, accurate diagnosis and holistic care are key to good clinical outcomes. OA often requires the intervention of multi-disciplinary teams, including allergists and ophthalmologists. In LMIC countries particularly, resource constraints are a barrier to full symptom control and the adverse effects of OA on health and QoL are grossly under-appreciated.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

This article has been peer reviewed.

REFERENCES

- Leonardi A, Bogacka E, Fauquert JL, Kowalski ML, et al. Ocular allergy: Recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy* 2012;67(11):1327–1337.
- Leonardi A SD. The management of ocular allergy. *Allergy* 2019;1(1–2):5–8.
- Amod R. Immunology of Allergic Eye Disease. *Curr Allergy Clin Immunol* 2006;19(2):70–73.
- Mashige K. A review of the management of ocular allergy: Peer review article. *Curr Allergy Clin Immunol* [Internet]. 2015;28(4):275–81. Available from: http://journals.co.za/docserver/fulltext/caci/28/4/caci_v28_n4_a8.pdf?expires=1515928684&id=id&accname=guest&checksum=8C4722FE10AEB5032BCCE03C839457C7.
- La Rosa M, Lionetti E, Reibaldi M, Russo A, et al. Allergic conjunctivitis: A comprehensive review of the literature. *Ital J Pediatr* 2013;39(1):1–8.
- Gomes PJ. Trends in prevalence and treatment of ocular allergy. *Curr Opin Allergy Clin Immunol* 2014;14(5):451–456.
- Tham EH, Lee AJ, Van Bever H. Aeroallergen sensitization and allergic disease phenotypes in Asia. *Asian Pacific J Allergy Immunol* 2016;34:181–189.
- Björkstén B, Clayton T, Ellwood P, Stewart A, et al. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 2008;19(2):110–124.
- Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol* 2007;18(7):560–565.
- S, Resnikoff CG. Limbal vernal conjunctivitis in the tropics. *Rev Int Trach* 1988;3(4):53–71.
- Kyei S, Tettey B, Asiedu K, Awuah A. Knowledge and awareness of ocular allergy among undergraduate students of public universities in Ghana. *BMC Ophthalmol* [Internet] 2016;16(1):1–8.
- De Smedt S, Nkurikiye J, Fonteyne Y, Hogewoning A, et al. Vernal keratoconjunctivitis in school children in Rwanda and its association with socio-economic status: A population-based survey. *Am J Trop Med Hyg* 2011 Oct;85(4):711–717.
- Visser L. HIV and the eye. *CME* 2013;31(4):143–146.
- Dahan E, Appel R. Vernal keratoconjunctivitis in the black child and its response to therapy. *Br J Ophthalmol* 1983;67(10):688–692.
- Moukouri dit Nyolo E, Nyolo D, McMoli T NK. Tropical endemic limbal conjunctivitis in Cameroon patients. Apropos of 819 cases in Yaounde. *Bull Soc belge Ophtalmol* 1993;86(2):120–124.
- Ukponmwan CU. Vernal keratoconjunctivitis in Nigerians: 109 consecutive cases. *Trop Doct* 2003;33(4):242–245.
- Botha M, Basera W, Facey-Thomas HE, Gaunt B, et al. Rural and urban food allergy prevalence from the South African Food Allergy (SAFFA) study. *J Allergy Clin Immunol* [Internet] 2019;143(2):662–668.
- Gray CL. Food allergy in South Africa. *Curr Allergy Asthma Rep* 2017;17(6):35.
- Green RJ, Hockman M, Friedman R, Davis M, et al. Chronic rhinitis in South Africa: Update 2013. *S Afr Med J* 2013;103(6):419–422.
- Abo-Ali FH, Farres MN, Shahin RY, Eissa AM, et al. Skin-prick test reactivity to aeroallergens among Egyptian patients with Isolated Allergic Conjunctival Disease. *Egypt J Immunol* 2015;22(2):41–47.
- Brožek JL, Bousquet J, Agache I, Agarwal A, et al. Allergic rhinitis and its impact on Asthma (ARIA) guidelines – 2016 revision. *J Allergy Clin Immunol* 2017;140(4):950–958.
- Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. *Curr Opin Allergy Clin Immunol* 2007;7(5):436–441.
- Leonardi A, Doan S, Fauquert JL, Bozkurt B, et al. Diagnostic tools in ocular allergy. *Allergy Eur J Allergy Clin Immunol* 2017;72(10):1485–1498.
- Kumar S. Vernal keratoconjunctivitis: A major review. *Acta Ophthalmol* 2009;87(2):133–147.
- Chen JJ, Applebaum DS, Sun GS, Pflugfelder SC. Atopic keratoconjunctivitis: A review. *J Am Acad Dermatol* 2014;70(3):569–575.
- De Smedt S, Wildner G, Kestelyn P. Vernal keratoconjunctivitis: An update. *Br J Ophthalmol* 2013;97(1):9–14.
- Sacchetti M, Baiardini I, Lambiase A, Aronni S, et al. Development and testing of the quality of life in children with Vernal Keratoconjunctivitis questionnaire. *Am J Ophthalmol* 2007;144(4):557–563.
- Armentia A, Sanchis E, Montero JA. Component-resolved diagnostics in vernal conjunctivitis. *Curr Opin Allergy Clin Immunol* 2016;16(5):498–504.
- Leonardi A, Borghesan F, Faggian D, Plebani M. Microarray-based IgE detection in tears of patients with vernal keratoconjunctivitis. *Pediatr Allergy Immunol* 2015;26(7):641–645.
- Leonardi A, Palmigiano A, Mazzola EA, Messina A, et al. Identification of human tear fluid biomarkers in vernal keratoconjunctivitis using iTRAQ quantitative proteomics. *Allergy Eur J Allergy Clin Immunol* 2014;69(2):254–260.
- Bore M. Managing ocular allergy in resource-poor settings. *Community Eye Heal J*. 2016;29(95):47–49.
- Caputo R, Versaci F, Pucci N, De Libero C, et al. Very low prevalence of keratoconus in a large series of Vernal Keratoconjunctivitis patients. *Am J Ophthalmol* 2016;172:64–71.
- Sofi RA, Mufti A. Vernal Keratoconjunctivitis in Kashmir: A temperate zone. *Int Ophthalmol* 2016;36(6):875–879.
- Occasi F, Zicari AM, Petrarca L, Nebbioso M, et al. Vernal Keratoconjunctivitis and immune-mediated diseases: One unique way to symptom control? *Pediatr Allergy Immunol* 2015 May;26(3):289–291.
- Doan S, Amat F, Gabison E, Saf S, et al. Omalizumab in severe refractory Vernal Keratoconjunctivitis in children: Case series and review of the literature. *Ophthalmol Ther* 2017;6(1):195–206.
- González-Pérez R, Poza-Guedes P, Matheu V, Sanchez-Machín I. Rapid clinical response to omalizumab in severe Atopic Keratoconjunctivitis. *J Allergy Clin Immunol* 2016;137(2):AB161.
- Mahdy RA, Nada WM, Marei AA. Subcutaneous allergen-specific immunotherapy versus topical treatment in vernal keratoconjunctivitis. *Cornea* 2012;31(5):525–528.