Vernal keratoconjunctivitis is an ocular allergy that is common in the pediatric age group. It is often chronic, severe and non-responsive to the available treatment options. Management of these children is difficult and often a dilemma for the practitioner. There is a need to simplify and standardize its management. To achieve this goal, we require a grading system to judge the severity of inflammation and an algorithm to select the appropriate medications. This article provides a simple and practically useful grading system and a stepladder algorithm for systematic treatment of these patients. Use of appropriate treatment modalities can reduce treatment and disease related complications.

**Keywords**: vernal keratoconjunctivitis • allergy • grading • treatment

Allergic conjunctivitis comprise of a spectrum of diseases affecting the ocular surface. These include two acute disorders, seasonal allergic conjunctivitis and perennial allergic conjunctivitis and two chronic diseases, vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis. Giant papillary conjunctivitis classified in ocular allergies is not a true allergy.

The mast cell mediated ocular surface inflammation results in itching, tearing, redness, photophobia, lid swelling and conjunctival chemosis during the acute phase. Chronic surface inflammation due to a classic late-phase response with associated eosinophilia and neutrophilia develops in the more severe forms of disease. These patients often have severe symptoms and ocular surface damage and remodeling and this can lead to visual loss due to corneal scarring and limbal deficiency.

For chronic and severe disease there are no safe and effective treatment options. Topical steroids are currently the mainstay of therapy in these patients but are associated with an increased risk of cataract and glaucoma. Thus there is a need for developing better management strategies for these patients.

VKC in India (Figure 1) seems to show an increase and we see more of early onset paediatric disease, adult disease, severe and chronic disease and more complications due to steroid abuse. Limited epidemiologic data on VKC in India is available. VKC in the Indian subcontinent is essentially similar to the pattern described in other tropical countries. The pattern is predominantly a mixed form of disease (72%) with significant number of patients having chronic perennial form (36%) and lesser association with atopy and systemic allergies as compared to patients in temperate zones. Treatment-associated complications are seen more often (Cataract 6% and Glaucoma 4%). Persistent disease beyond 20 years of age is seen more often (12%).

**Limitations In the Current Options In Management**

Medical treatment options include lubricants, antihistamines and mast cell stabilizers, cyclosporine and tacrolimus, Mitomycin C, topical steroids and oral steroids in severe cases. Steroid drops are the most effective medication that we have in our armamentarium but also the most unsafe especially with chronic and unmonitored usage. It unfortunately is the first drug of choice by default for many eye care practitioners.

Limitations to current management strategies are the lack of well-defined management guidelines. The choice of medications may vary greatly for
the same severity of disease from physician to physician. This is often because of a lack of grading systems to gauge and classify the severity of VKC and standard guidelines to suggest the most appropriate safe therapy. Inadequate counseling and unrealistic expectations often result in overuse, misuse, and self-use of steroids and it is not uncommon to see patients with steroid related complications. Over medication with steroids can cause loss of vision due to steroid related complications while under medication and persistent inflammation can also cause vision loss due to corneal scarring and stem cell damage. (Figure 2). A delicate balance between the use of medications and side effects needs to be tailored to restrict tissue damage and also avoid medication related complications.

Vernal Keratoconjunctivitis in India

Grading of VKC

Bonini et al have described a 5 tier grading system (Table 1) based on presence or absence of symptoms, photophobia and extent of corneal involvement. Moreover, this system does not take into account the various presentations of the disease process, severity of the disease process and also the periodicity of the disease. As an ophthalmologist we are concerned about patients with corneal involvement and there are only 2 grades to sub classify these patients.

A more refined grading system is provided herewith which is simple to use and is based on clinical signs. It will help the clinician to grade the severity of disease and periodicity of disease both of which are crucial to help plan the most appropriate management. The grading needs to be repeated at every visit as treatment and seasonal fluctuations typically alter the severity of allergic disease and this may change the management chosen. Another benefit of this system is that it forces you to try and correctly assess and document clinical findings at every visit and tailor the therapy accordingly.

The bulbar and tarsal conjunctiva and the cornea and limbus are evaluated, and the severity of involvement is graded clinically. It is usually possible to classify the disease severity into mild, moderate, severe, and blinding categories (Figure 3). Patients may have findings that do not fall into the same severity. In these instances the corneal findings are given more importance over conjunctival findings. For example a patient having giant papillae but no corneal or limbal involvement may still be classified for treatment purpose as mild disease, because the papillae may be inactive and not causing any corneal erosions. The grading is done in both eyes independently. Periodicity of disease is an important parameter to be taken into consideration while planning treatment. For example a child who has two or three episodes in a year may be safely given short courses of mild steroids but in a child with chronic disease, it may not be a good option to give chronic continuous steroid therapy.

Intermittent disease periodicity is defined as inflammation free intervals of greater than 2 to 3 months during which patient are off medications. This would mean a maximum of 3 to 4 episodes in a year, which remit on therapy.

Chronic disease periodicity is defined as inflammation free intervals of less than one month during which patient is off medications. This would mean that patient has continuous ongoing inflammation, which possibly recurs on attempting to stop or taper therapy. Such a patient has chronic disease all throughout the year.
2 were treated with anti allergic eye drops while grade 3 & 4 were treated with additional topical steroids. This simplistic approach is highly inadequate to manage a complex problem like VKC. It does not give any guidelines for other treatment options for VKC such as the use of topical cyclosporine and promotes the usage of only topical steroids in patients with corneal involvement. The stepladder approach (Figure 4,5) aims to provide the safest possible way to control allergic inflammation based on its severity and periodicity.5

This means that we use less potent medications in mild disease and switch to more potent medications for the more severe forms of disease. Treatment and natural fluctuations will alter the grade of disease and will necessitate alterations in therapy. Typically as the allergy wanes we go down the ladder and use safer medications and as it worsens we go up the ladder using more potent medications.

**Mild disease:** Patients will be symptomatic (redness, itching) and on examination have congestion and fine velvety papillae, but no corneal involvement. They should be treated with allergen avoidance (A), lubricants (L), antihistaminics (H) and mast cell stabilisers (M). Steroids should be avoided especially in the absence of any corneal involvement.

**Moderate disease:** Patients with corneal involvement in the form of fine punctate erosions and or limbal inflammation and thickening of less than 6 clock hours are classified as moderate disease. They require add on therapy (in addition to ALHM) based on periodicity of disease. In intermittent disease short pulses of mild surface acting steroids (eg. Lotepredenol) can be given to tackle the recurrences while in chronic disease long term continuous therapy with topical 0.5% cyclosporine (C) is initiated.

**Severe disease:** Patients with large papillae or cobblestones, macroerosions and severe limbal inflammation greater than 6 clock hours are classified as severe disease. They require to be treated initially with pulse of potent topical steroids (along with ALHM) and then maintained with chronic 0.5% - 1% cyclosporine therapy. Patients can require an additional maintenance therapy with low dose topical surface steroid often once a day or alternate day.

**Blinding disease:** Patients with active shield ulcers, limbal inflammation with pannus and limbal stem cell deficiency and extremely active large cobblestones are the most difficult to treat. These patients may need continuous use of potent steroids in addition to ALHMC. They need to be more closely monitored for cataract and glaucoma. A logbook of daily steroid usage may be useful in these patients. They may also need supratarsal steroids and debridement for shield ulcers. Systemic steroids may be needed for very refractory inflammation. These children often have associated atopy and allergies elsewhere (asthma / skin / rhinitis etc) which

---

**Table 1: Clinical Grading of VKC and tailored treatment**

| Grade   | Findings                                      | Treatment                                      |
|---------|-----------------------------------------------|------------------------------------------------|
| 0 Quiescent | Absence of symptoms                          | No treatment                                  |
| 1 Mild  | Symptoms but no corneal Involvement            | Antiallergic drops occasionally               |
| 2 Moderate | Symptoms with photophobia but no corneal involvement | Antiallergic drops daily                       |
| 3 Severe | Symptoms, Photophobia Mild to moderate SPK     | Antiallergic eye drops daily with pulsed low dose topical steroid |
|          | Symptoms, Photophobia Diffuse SPK or Corneal Ulcer | Pulsed high dose topical steroid eventually associated with surgical removal of corneal plaque |

**SPK = Superficial Punctate Keratitis**
are equally severe. Omalizumab, Oral cyclosporine therapy and intravenous immunoglobulins have also been reported to be effective in these patients especially if they repeatedly require systemic steroid courses.\(^5\)\(^,\)\(^7\)

**Surgery**

Patients with severe and blinding disease may also require surgical interventions such as superficial keratectomy for shield ulcer plaques, cryotherapy for refractory cobblestones, excision with or without mitomycin C for refractory cobblestones, amniotic membrane grafts and reconstructive surgery such as limbal stem cell transplants. The decision for this may be taken on a case-to-case basis by the treating ophthalmologist preferably a cornea specialist.

**Cyclosporine A**

Cyclosporine A is effective in controlling ocular inflammation by blocking Th2 lymphocyte proliferation and interleukin 2 production. It also inhibits histamine release from mast cells and basophils and, through a reduction of IL-5 production; it may reduce the recruitment and the effects of eosinophils on the conjunctiva.\(^8\) Moreover, the therapeutic efficacy of cyclosporine in VKC, a conjunctival hyperproliferative disorder,\(^9\) seems to be related to the drug's efficacy in reducing conjunctival fibroblast proliferation rate and IL-1β production.\(^8\) Multiple studies on the efficacy of topical CsA (0.05–2%) for treating vernal keratoconjunctivitis have consistently shown a beneficial effect of the drug and its steroid-sparing effect.\(^10-13\) They are safe and effective and have been used up to a 7 year period in VKC patients.\(^8\) Unfortunately the commercially available drops (0.05% and 0.1%) are effective only in very mild forms of disease. Cyclosporine drops at higher concentrations can be easily formulated by mixing the commercially available injection cyclosporine (50mg/ml) with artificial tears. These are better tolerated than the oil based formulations and are stable for up to a month.\(^14\) A concentration of 0.5% provides an optimum balance between efficacy and tolerance. 1% strength can be used in severe cases however concentrations up to 2% have been described in literature.\(^12,13\) Since they need to be prepared everytime the patient has to return back for the drops to the clinician and this gives an opportunity to follow up and examine them, which is not possible when patients on steroids are lost to follow up.

**Tacrolimus**

Tacrolimus (FK-506) is a macrolide antibiotic that has potent immunomodulatory properties. It acts primarily on T-lymphocytes by inhibiting production of cytokines, particularly IL-2, IL-5, IL-10, TNF-α and IFN-γ. Tacrolimus (FK-506) acts like cyclosporine A and inhibits activation of T cells, and also inhibits IgE-dependent histamine release from mast cells and basophils.\(^15\) Both drugs act on their target cells via cyclophyllin receptors. Tacrolimus ointment in 0.03% and 0.1% are available as dermatological preparations. It has been tried in refractory anterior segment inflammatory disorders including VKC with good results.\(^16\) Tacrolimus 0.1% has been safely and successfully used for three years in patients with VKC.\(^17\) The same group recently reported a comparative study of cyclosporine 2% vs. Tacrolimus 0.1% and reported similar efficacy.\(^18\)

Since the US Food and Drug Administration put a warning on the use of Tacrolimus and Pimecrolimus ointment in the treatment of atopic dermatitis for its potential to cause cancer,\(^19\) it has advocated that it be used as a second line treatment and is not recommended before 2 years of age. This has hindered efforts to develop Tacrolimus ointment for ophthalmological use. Tolerance to tacrolimus ointment is often poor when applied to the conjunctival sac, however transdermal action by applying it to the eyelids is an effective option in these patients. It has the advantage that it is commercially available and has a safety profile similar to cyclosporine A. However long term data with regard to safety needs to be studied with Tacrolimus. It would be a good alternative option to cyclosporine especially for patients who cannot come back regularly for preparation of cyclosporine drops. Improvement in the available formulations and long term safety data might enhance the use of this drug for VKC.

**Conclusions**

There is a need for better understanding and management of allergic eye disease. Grading of severity of disease and periodicity of disease can be very useful for deciding the appropriate line of management. Topical Cyclosporine in higher concentrations and Tacrolimus ointment are useful steroid sparing agents that are underutilized and will help to safely control patients with moderate to severe allergy. The stepladder approach is a novel way of managing these difficult cases in day-to-day practice. Severe and refractory VKC is a serious condition with significant morbidity and may not still be satisfactorily addressed by currently available treatment options and is a matter of ongoing research.

**Financial & competing interest disclosure**

The authors do not have any competing interests in any product/ procedure mentioned in this study. The authors do not have any financial interests in any product / procedure mentioned in this study.

**References**

1. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol 2005; 115:118-22.
2. Katelaris CH. Ocular allergy in the Asia Pacific region. Asia Pac Allergy. 2011; 1:108-14.
3. Saboo US, Jain M, Reddy JC, Sangwan VS. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care center in India. Indian J Ophthalmol 2013; 61:486-9.
4. Sacchetti M, Lambiase A, Mantelli F, Deligianni V, Leonardi A, Bonini S. Tailored approach to the treatment of vernal keratoconjunctivitis. Ophthalmology 2010; 117:1294-9.
5. Gokhale NS, Samant R, Sharma V. Oral cyclosporine therapy for refractory severe vernal keratoconjunctivitis. Indian J Ophthalmol. 2012; 60:220-3.
6. Williams PB, Sheppard JD Jr. Omalizumab: a future innovation for treatment of severe ocular allergy? *Expert Opin Biol Ther* 2005; 5:1603-9.

7. Derriman L, Nguyen DQ, Ramanan AV, Dick AD, Tole DM. Intravenous immunoglobulin (IVIg) in the management of severe refractory vernal keratoconjunctivitis. *Br J Ophthalmol* 2010; 94:667-9.

8. Leonardi A. Emerging drugs for ocular allergy. *Expert Opin Emerg Drugs* 2005; 10:505-20.

9. Leonardi A, Borghesan F, De Paoli M, Plebani M, Secchi AG. Procollagens and inflammatory cytokine concentrations in tarsal and limbal vernal keratoconjunctivitis. *Exp Eye Res* 1998; 67:105-12.

10. Tesse R, Spadavecchia L, Fanelli P, Rizzo G, Procoli U, Brunetti L, et al. Treatment of severe vernal keratoconjunctivitis with 1% topical cyclosporine in an Italian cohort of 197 children. *Pediatr Allergy Immunol* 2010; 21:330-5.

11. Keklikci U, Soker SI, Sakalar YB, Unlu K, Ozekinci S, Tunik S. Efficacy of topical cyclosporin A 0.05% in conjunctival impression cytology specimens and clinical findings of severe vernal keratoconjunctivitis in children. *Jpn J Ophthalmol* 2008; 52:357-62.

12. Kiliç A, Gürler B. Topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis. *Can J Ophthalmol* 2006; 41:693-8.

13. Pucci N, Caputo R, Mori F, De Libero C, Di Grande L, Massai C, Bernardini R, Novembre E. Long-term safety and efficacy of topical cyclosporine in 156 children with vernal keratoconjunctivitis. *Int J Immunopathol Pharmacol* 2010; 23:865-71.

14. Fiscella RG, Le H, Lam TT, Labib S. Stability of cyclosporine 1% in artificial tears. *J Ocul Pharmacol Ther* 1996; 12:1-4.

15. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporine A and FK 506. *Immunol Today*. 1992; 13:136-42.

16. Joseph MA, Kaufman HE, Insler M. Topical tacrolimus ointment for treatment of refractory anterior segment inflammatory disorders. *Cornea* 2005; 24:417-20.

17. Pacharn P, Visitsunthorn N, Jirapongsananuruk O, Vichyanond P. Vernal Keratoconjunctivitis (VKC) treated with 0.1% FK-506 ophthalmic ointment: result of three years follow-up. *J Allergy Clin Immunol* 2007; 119:S153.

18. Labcharoenwongs P1, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P, Saengin P, Vichyanond P. A double-masked comparison of 0.1% tacrolimus ointment and 2% cyclosporine eye drops in the treatment of vernal keratoconjunctivitis in children. *Asian Pac J Allergy Immunol* 2012; 30:177-84.

19. Ring J1, Möhrenschlager M, Henkel V. The US FDA ‘black box’ warning for topical calcineurin inhibitors: an ongoing controversy. *Drug Saf* 2008; 31:185-98.