Ophthalmology Practice

# Systematic approach to managing vernal keratoconjunctivitis in clinical practice: Severity grading system and a treatment algorithm

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Vernal keratoconjunctivitis is an ocular allergy that is common in the pediatric age group. It is often chronic, severe, and nonresponsive 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.

**Key words:** Allergy, grading, treatment algorithm, vernal keratoconjunctivitis

**Access this article online**

**Website:** www.ijo.in

**DOI:** 10.4103/0301-4738.179727

**Quick Response Code:**

Allergic conjunctivitis comprises of a spectrum of diseases affecting the ocular surface. These include two mild forms, seasonal allergic conjunctivitis and perennial allergic conjunctivitis and two severe forms, vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis.[1] 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 occurs in the more severe forms of disease. These patients have severe disabling symptoms, and chronic ocular surface damage 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 in most practices but are associated with an increased risk of cataract and glaucoma. Thus, there is a need for developing better management strategies for these patients.

Limited epidemiologic data on VKC in India is available.[2] VKC in the Indian subcontinent is essentially similar to the pattern described in other tropical countries.[3] The pattern is predominantly a mixed form of disease (72%) with a significant number of patients having a 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%).[3]

## Limitations in the Current Literature and Management

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.

Medical treatment options include lubricants, antihistaminics 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.

Sacchetti *et al*. described a tailored approach for the treatment of VKC based on their grading system.[4] A five-tier grading system is described based on the presence or absence of symptoms, photophobia, and extent of corneal involvement. However, this system does not take into account the various

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Manuscript received: 23.09.14; Revision accepted: 19.01.16



**Cite this article as:** Gokhale NS. Systematic approach to managing vernal keratoconjunctivitis in clinical practice: Severity grading system and a treatment algorithm. Indian J Ophthalmol 2016;64:145-8.

presentations of the disease process, severity of the disease process, and also the periodicity of the disease. Grade 1 and 2 were treated with anti-allergic eye drops while Grade 3 and 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.

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. Overmedication 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. 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.

## Grading of Vernal Keratoconjunctivitis

A grading system is provided herewith [Table 1] 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 will change the further management chosen. Another benefit of this system is that it is essential to correctly assess and document clinical findings at every visit and tailor the therapy accordingly.

It is usually possible to classify the disease severity into mild, moderate-intermittent, moderate-chronic, severe, and blinding subtypes. 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 large papillae but no corneal or limbal involvement may still be classified for treatment purpose as a mild disease because the papillae may be inactive and not causing any corneal erosions. The grading is done in both eyes independently.

The 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 all year long disease, it may not be a good option to give chronic continuous steroid therapy.

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

Chronic disease periodicity is defined as inflammation free intervals of <1 month during which the 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.

## Treatment Algorithm

The treatment algorithm [Table 2] aims to provide the safest possible way to control allergic inflammation based on its

**Table 1: Clinical grading system**

| Clinical finding | Mild | Moderate intermittent* | Moderate chronic# | Severe | Blinding |
|---|---|---|---|---|---|
| Symptoms | ✓ | ✓ | ✓ | ✓ | ✓ |
| Papillae | ✓ | ✓ | ✓ | ✓ | ✓ |
| Horner-Trantas dots | × | ✓ | ✓ | ✓ | ✓ |
| Fine SPEE | × | ✓ | ✓ | ✓ | ✓ |
| Focal limbal inflammation (<6 clock hours) | × | ✓ | ✓ | ✓ | ✓ |
| Cobblestones | × | × | ✓ | ✓ | ✓ |
| Annular limbal inflammation (>6 clock hours) | × | × | × | ✓ | ✓ |
| Coarse SPEE/PEK | × | × | × | ✓ | ✓ |
| Conjunctival granulomas | × | × | × | ✓ | ✓ |
| Limbal deficiency-pannus | × | × | × | ✓ | ✓ |
| Macroerosions | × | × | × | ✓ | ✓ |
| Shield ulcer | × | × | × | × | ✓ |
| LSCD with conjunctivalization vascular corneal/ tarsal scarring | × | × | × | × | ✓ |

*Intermittent periodicity: <4 episodes per year with complete remission, #Chronic periodicity: All round the year. Remission period <1 month. SPEE: Superficial punctate epithelial erosions, SPK: Superficial punctate keratitis, LSCD: Limbal stem cell deficiency

**Table 2: Treatment algorithm**

| Medication | Mild | Moderate intermittent | Moderate chronic | Severe | Blinding |
|---|---|---|---|---|---|
| Plaque debridement | × | × | × | × | ✓ |
| Cryotherapy excision±MMC | × | × | × | × | ✓ |
| Oral steroid oral CSA | × | × | × | × | ✓ |
| CSA 2% | | | | | ✓ |
| Supratarsal steroids | × | × | × | ✓ | ✓ |
| Tacrolimus ointment | × | × | × | ✓ | ✓ |
| Potent steroids | × | × | × | ✓ | ✓ |
| CSA 1% | × | × | × | ✓ | ✓ |
| CSA 0.5% | × | × | ✓ | × | × |
| Low-frequency loteprednol | × | × | ✓ | × | × |
| Loteprednol pulses | × | ✓ | × | × | × |
| Antihistaminics mast cell stabilizers | ✓ | ✓ | ✓ | ✓ | ✓ |
| Lubricants | ✓ | ✓ | ✓ | ✓ | ✓ |
| Avoidance | ✓ | ✓ | ✓ | ✓ | ✓ |

MMC: Mitomycin C, CSA: Cyclosporine A

severity and periodicity. This means that we use less potent medications in mild disease and switch to more potent medications for the more severe forms of disease.[5] Treatment and natural fluctuations will alter the grade of disease and will necessitate alterations in therapy. Typically as the allergy waxes and wanes, the severity grading will change and accordingly the treatment is tailored.

### Mild disease

Patients will be symptomatic (redness and 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 stabilizers (M). Steroids should be avoided in the absence of any corneal involvement.

### Moderate disease (intermittent and chronic)

Patients with corneal involvement in the form of fine punctate erosions, Horner–Trantas dots and focal limbal inflammation, and thickening of <6 clock hours are classified as a moderate disease. They require add-on therapy (in addition to ALHM) based on the periodicity of disease. In intermittent disease short pulses of mild surface acting steroids (e.g., loteprednol) can be given to tackle the recurrences. In chronic disease, long-term continuous therapy with topical 0.5% cyclosporine (C) is initiated and for persistent inflammation low-frequency mild steroids (typically once or alternate day once) can be added intermittently.

### Severe disease

Patients with large active cobblestones, coarse erosions or keratitis, macroerosions, and severe limbal inflammation >6 clock hours are classified as a severe disease. These patients may have evidence of limbal deficiency in the form of pannus and postinflammatory scarring. They require to be treated initially with the pulse of potent topical steroids (along with ALHM) and then maintained with chronic 1% cyclosporine therapy. Tacrolimus 0.03% ointment can also be used either transdermally or in the eye based on tolerance. Patients can require an additional maintenance therapy with low-frequency topical steroids (typically once or alternate day once).

### Blinding disease

Patients with extremely active large cobblestones, active shield ulcers, severe annular limbal inflammation, limbal stem cell deficiency manifesting as extensive conjunctivalization, limbal scarring, and extensive corneal scarring and are the most difficult to treat. These patients may need continuous use of potent steroids in addition to ALHMC. Cyclosporine 2% drops and tacrolimus 0.03% ointment can be used in combination. A log book of daily steroid usage may be useful in these patients. These patients need to be more closely monitored for complications such as infection, cataract, and glaucoma. 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 are often 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]

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

## Steroid Sparing Agents

It is essential to promote the use of steroid-sparing agents such as topical cyclosporine A and tacrolimus in patients with VKC and will be described briefly.

### Cyclosporine A

Cyclosporine A is effective in controlling ocular inflammation by blocking Th2 lymphocyte proliferation and interleukin 2 (IL-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 VKC 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 years 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 (50 mg/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. One percent of strength can be used in severe cases; however, concentrations up to 2% have been described in the literature.[12,13] Since they need to be prepared every time 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. Recently 2% Cyclosporine drops are being marketed in India by Aurolab Pharma as Aurosporine 2% and can also be used in these patients.

### 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-3, IL-5, tumor necrosis factor-α, and interferon-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 3 years in patients with VKC.[17] The same group recently

reported a comparative study of cyclosporine 2% versus 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. However Tacrolimus eye ointment (0.03% and 0.1%) have recently been introduced in the Indian market. 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 the 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 the 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 support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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