ALLERGIC CONJUNCTIVITIS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Original Allergic Conjunctivitis Clinical Guidance- Issued July 2020

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Abbreviations

AC	Allergic Conjunctivitis
ACD	Allergic Conjunctival Disease
AKC	Atopic Keratoconjunctivitis
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CsA	Ciclosporin A
EMA	European Medicines Agency
FDA	Food and Drug Administration
GPC	Giant Papillary Conjunctivitis
HAS	Haute Autorite de Sante
HTA	Health Technology Assessment
IOP	Intraocular Pressure
IQWIG	Institute for Quality and Efficiency in Health Care
LE	Level of Evidence
LSCD	Limbal Stem Cell Deficiency
NICE	National Institute for Health and Care Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
OBS	Observation
PAC	Perennial Allergic Conjunctivitis
PMDA	Pharmaceuticals and Medical Devices Agency
SAC	Seasonal Allergic Conjunctivitis
SC	Subcutaneous
SFDA	Saudi Food and Drug Authority
VKC	Vernal Keratoconjunctivitis

Executive Summary

Allergic conjunctivitis is a common eye problem that affects more than 20% of people. It is a reaction of the outer lining of the eyeball (conjunctiva) to things in the environment to which a person is allergic (allergens). These allergens can encompass substances such as dust, pollen, animal dander, and sometimes even certain medications. When the eyes encounter these allergens, they can exhibit symptoms like redness, inflammation, excessive tearing, itchiness, or swelling. Although these symptoms can look like the signs of an infection, allergic conjunctivitis is not an infection and is not contagious[1].

Allergic conjunctival disease (ACD) is defined as "a conjunctival inflammatory disease associated with a type I allergy accompanied by some subjective and objective symptoms." Conjunctivitis associated with type I allergic reactions is considered ACD even if other types of inflammatory reactions are involved[2].

ACD is classified into multiple disease types according to the presence or absence of proliferative changes, complicated atopic dermatitis, and mechanical irritation by foreign body. ACD is classified as follows: AC without proliferative change, AKC complicated with atopic dermatitis, VKC (Vernal keratoconjunctivitis) with proliferative changes, and GPC (Giant papillary conjunctivitis) induced by irritation of a foreign body. Allergic conjunctivitis is subdivided into SAC (Seasonal Allergic Conjunctivitis) and PAC (Perennial Allergic Conjunctivitis) according to the period of onset of the symptoms[2].

Allergic conjunctivitis symptoms may be: 1) Perennial (all year round) due to exposure to dust mite, animal dander, indoor and outdoor mold spores, and occasionally foods or food additives. 2) Seasonal due to airborne allergens such as pollen of grasses, trees, and weeds. Pollen allergy symptoms vary from day to day, depending on the weather, improving in wet weather, and worsening on hot windy days or after thunderstorms. There are also seasonal variations in some airborne mold spores, which may cause seasonal symptoms. Hence, Allergic conjunctivitis can be grouped into two types: ***seasonal*** *allergic conjunctivitis*, the seasonal form associated with seasonal allergies that usually occur during the spring and summer months, and sometimes during the fall and ***perennial*** *allergic conjunctivitis,* the perennial form that persists throughout the year[3].

Allergic conjunctivitis is usually bilateral with common eye symptoms and signs that include itching (the hallmark of allergic eye disease), foreign body sensation, serous or mucous discharge, conjunctival hyperemia, and tarsal papillary reaction. Symptoms can be differentiated into those that manifest primarily during the early or the late phase of the disease[4].

While allergic conjunctivitis typically doesn't impair vision, it does lead to significant discomfort and can greatly diminish the quality of life for affected individuals, particularly children and adolescents, who are more frequently afflicted by certain variations of the condition. In some cases, however, severe forms of the condition can negatively impact vision if they progress to a complicated stage and affect the cornea, potentially resulting in corneal scarring and the development of pannus. Therefore, it's crucial to diagnose these conditions early and administer appropriate treatment to enhance patients' quality of life, reduce the occurrence of relapses, and prevent potential complications[4].

Allergic conjunctivitis is a group of diseases caused by the ocular response to environmental allergens. They are common, affecting 10-20% of the population. Allergy rates are increasing and, at present, approximately 20% of the world population is affected by some form of allergy. Up to 40-60% of allergic patients have ocular symptomatology[4].

According to a survey published in the Oman Journal of Ophthalmology in February 2020 about the prevalence and causative agents of allergic conjunctivitis and its determinants in adult citizens of Western Saudi Arabia including adult population of Taif, Makkah, and Jeddah cities who were surveyed from 2017 to June 2018, the prevalence of AC was 70.5% (95% CI 70.4–70.6). On its basis, there could be as many as 2.07 million adult Saudis suffering from AC in the study area[5].

The economic burden of the disease is also increasingly recognized. This includes direct costs such as medications and visits to health care providers, as well as indirect costs such as missed days of work and decreased productivity while at work. Although no data are available related to the cost of AC specifically, the direct annual cost of allergic rhino conjunctivitis is estimated at $2–5 billion in the United States[6].

Diagnosis of conjunctivitis and differentiation between bacterial, viral, and noninfectious conjunctivitis (see table Differentiating Features in Acute Conjunctivitis) are usually clinical. In allergic conjunctivitis, eosinophils are present in conjunctival scrapings, which may be taken from the lower or upper tarsal conjunctiva; however, such testing is rarely indicated[7].

Identifying and eliminating the underlying cause of allergic conjunctivitis, when feasible, is the optimal course of action, particularly when allergy testing has confirmed the allergic trigger. For example:

- House dust mite minimization measures in the bedroom (removing carpet, using barrier encasing of pillows and mattress, washing bedding in hot water).
- Removing cats from the house for sensitive individuals.

It's also vital to rule out the presence of foreign objects like dust, wood chips, or insects. Symptoms of allergic conjunctivitis are typically mild to moderate and typically respond well to soothing measures like rinsing the eyes with cold water,

applying ice packs, and using cold water compresses. The application of topical lubricants can also assist in flushing allergens from the tear film. Nevertheless, in some instances, symptoms can be extremely severe and incapacitating, necessitating the use of medication.[8]

CHI issued allergic conjunctivitis guidelines in July 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates.

This report functions as an addendum to the prior CHI Allergic Conjunctivitis clinical guidance and seeks to offer guidance for the effective management of Allergic Conjunctivitis. It provides an **update on the Allergic Conjunctivitis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the new guidelines added to the report** such as Japanese guidelines for allergic conjunctival diseases [2020], Brazilian guidelines for the monitoring and treatment of pediatric allergic conjunctivitis [2022], Management of Vernal Keratoconjunctivitis in *Children* in the United Kingdom: A *Review* of the Literature and Current Best Practice Across Six Large United Kingdom Centers [2023], Novel Insights in the Management of Vernal Keratoconjunctivitis (VKC): European Expert Consensus Using a Modified Nominal Group Technique [2023], Management of vernal keratoconjunctivitis in *children* in Saudi Arabia [2020].

After carefully examining clinical guidelines and reviewing the SFDA drug list, there are no new SFDA registered drugs to include in the CHI formulary while removing - DEXPANTHENOL, SODIUM HYALURONATE - EBASTINE - ECTOIN, SODIUM HYALURONATE - GLYCERIN, SODIUM CARBOXYMETHYLCELLULOSE as they are no longer registered on the SFDA Drug List of September 2023. There have been no changes or updates made to any of the previously listed drugs in terms of drug information and prescribing edits since July 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Allergic Conjunctivitis therapeutic management.

Below is a table summarizing the major changes based on the different Allergic Conjunctivitis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Allergic Conjunctivitis

Management of Allergic Conjunctivitis		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Pediatric Allergic Conjunctivitis Nonpharmacological measures include general environmental measures to reduce exposure to allergens (e.g., elimination of domestic dust, fungi, and pollen) and specific actions, such as the use of cold-water compresses, preservative-free artificial tears, and local cleansing with saline solution to wash the allergens from the conjunctiva and to contract the conjunctival vessels to relieve edema and hyperemia. In addition, sunglasses can be used to prevent contact with suspended allergens and for photophobia relief.	Grade of recommendation: A	Brazilian Guidelines [2022]
Multiple-acting agents act as mast cell stabilizers, selective H1 receptor antagonists (**olopatadine** and **ketotifen**), and modulators of the anti-inflammatory activity of eosinophils. Some, such as **Epinastine**, act on H1 receptors (reducing itching) and H2 receptors (reducing vasodilation), whereas others, such as **alcaftadine**, also block H4 receptors. Multiple-acting agents have prompt and long-lasting effects and have proven more effective than fluorometholone in the treatment of SAC	Grade of recommendation: A	Brazilian Guidelines [2022]
Mast cell membrane stabilizers must be administered every 6 to 8 hours for at least 2 weeks; consequently, adherence to their use is generally low	Grade of recommendation: A	Brazilian Guidelines [2022]

Topical NSAIDs have proven efficacy against hyperemia and conjunctival itching. The use of topical NSAIDs in children is also limited by their burning sensation.	Grade of recommendation: A	Brazilian Guidelines [2022]
Topical ocular corticosteroids are not considered a first-choice therapy for AC, although drugs in lower concentrations (**fluorometholone**, **loteprednol**, and **rimexolone**) can be used to treat moderate inflammation. The drugs of choice for severe inflammation are **dexamethasone** and **prednisolone**	Grade of recommendation B	Brazilian Guidelines [2022]
Patients with severe allergic keratoconjunctivitis, giant papillae, intense limbic involvement, or recurrent corneal ulcers can be given a supratarsal injection of corticosteroids as an adjuvant treatment option. Satisfactory results can be achieved with injections of 0.4 to 0.5 mL of **dexamethasone phosphate** (4 mg/mL), **prednisolone acetate** (40 mg/mL), or **triamcinolone acetate** (10.5 mg/mL). Repeated injections may be indicated at intervals of approximately 6 months	Grade of recommendation: D	Brazilian Guidelines [2022]
First-generation H1 antihistamines are not recommended, because of their sedative effect and anticholinergic activity. Second-generation drugs (**desloratadine**, **ebastine**, **loratadine**, and **rupatadine**) have similar efficacy but a more manageable sedation profile and fewer adverse effects	Grade of recommendation: B	Brazilian Guidelines [2022]
Drug treatment is the preferred treatment for ACDs. The first option is antiallergic eye drops, which are the basic treatment for allergic conjunctivitis, followed by the differential use of steroid eye drops as	Not graded	Japanese Guidelines [2020]

necessary according to the severity. For severe ACDs (AKC and VKC), additional use of immunosuppressive eye drops, steroid oral medicines, sub-tarsal conjunctival steroid injection and surgical treatment such as papillary resection should be considered.		
Eye drops: When a sufficient effect cannot be obtained by antiallergic eye drops only, steroid eye drops with a titer corresponding to the severity of inflammation are combined.	Not graded	Japanese Guidelines [2020]
Oral medicines: Medicines are used for pediatric and other patients for whom sub-tarsal conjunctival injection is difficult and for patients with corneal epithelial defect. The standard administration period is 1-2 weeks in consideration of its side effects. It is necessary to treat patients with caution for its systemic side effects in cooperation with internists and pediatricians.	Not graded	Japanese Guidelines [2020]
Eye ointments: When a sufficient effect is not obtained by antiallergic eye drops only or steroid eye drops cannot be used, ointments are used before bedtime.	Not graded	Japanese Guidelines [2020]
Triamcinolone acetonide or **betamethasone suspension** is injected to the sub-tarsal conjunctiva of the upper eyelid in intractable or severe cases. With caution for the elevation of intraocular pressure, it is desirable to avoid repeated use or the application to children aged <10 years	Not graded	Japanese Guidelines [2020]
At present, 2 kinds of immunosuppressive eye drops (**cyclosporine** and **tacrolimus**) have been approved as treatment drugs for	Not graded	Japanese Guidelines [2020]

VKC, with an expected similar or even superior effect to the steroid eye drops.		
Surgical treatment: For cases where symptoms are not alleviated by drug treatment and conjunctival papillary hyperplasia progresses to cause worsened corneal epithelium disorder, a tarsal conjunctival resection, including the papillae may be performed. While the treatment effect is immediate, it may recur in some cases. Although corneal plaques may be removed by surgical curettage, the treatment is performed only when the pathologic condition has been alleviated	Not graded	Japanese Guidelines [2020]
VKC: As first-line pharmacological therapy, dual-acting agents (e.g., **olopatadine, azelastine hydrochloride, epinastine, ketotifen**) may be considered rather than monotherapy with antihistamines or mast cell stabilizers (e.g., **sodium cromoglycate, nedocromil, lodoxamide**), depending on formulary, local recommendations, and availability.	Not graded	European Consensus, 2023
'High-potency' topical corticosteroids (e.g., **dexamethasone**), used as a pulse therapy for 3–5 days without tapering, could be more efficacious in resolving exacerbations and less likely to increase IOP than the longer-term use of 'soft' corticosteroids.	Not graded	European Consensus, 2023
Topical immunomodulators, such as CsA (**Ciclosporin A**), should be taken into consideration for patients dealing with moderate to severe or persistent VKC or those who are corticosteroid-dependent	Not graded	European Consensus, 2023
• Rubbing itchy eyes can make the condition worse (with advice on a 'no-touch zone')	Not graded	European Consensus, 2023

• Sunlight, wind, salty water, dust, and heat can exacerbate VKC, so the use of sunglasses, hats, visors, and swimming goggles may be considered. • An air-filtration system in the home may provide relief. • Common allergens can exacerbate VKC, and frequently washing the hands, face and hair can reduce exposure to these allergens. • Cold compresses and preservative-free artificial tears can provide symptomatic relief. • Adherence to treatment is important; it is important to be aware of the risks associated with the long-term use of corticosteroids and to promptly report any adverse events; and how to optimize the use of topical CsA.		

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Allergic Conjunctivitis clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Allergic Conjunctivitis report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the July 2020 CHI Allergic Conjunctivitis Report and the corresponding recommendations:

- There are no updated versions of the old guidelines.

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 Conjunctivitis a systematic review of diagnosis and treatment [2013] American Medical Association	N/A*
1.2 Conjunctivitis preferred practice pattern [2018] by the American Academy of Ophthalmology	N/A*
1.3 Optometric clinical practice guideline care of the patient with conjunctivitis [American Optometric Association 2010]	N/A*
1.4 Diagnosis and management of red eye in primary care [2010 American Family Physician]	N/A*
1.5 Diagnosing and managing allergic conjunctivitis in childhood: the allergist's perspective [2019]	N/A*
1.6 A contemporary look at allergic conjunctivitis [allergy, asthma & clinical immunology 2020]	N/A*

*****: *No updated versions available*

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Allergic Conjunctivitis report, along with their recommendations.

Table 2. List of Additional Guidelines

Additional Guidelines
Section 1.2.1 Brazilian guidelines for the monitoring and treatment of pediatric allergic conjunctivitis[9]
Section 1.2.2 Japanese guidelines for allergic conjunctival diseases 2020[2]
Section 1.2.3 Management of Vernal Keratoconjunctivitis in Children in the United Kingdom: A Review of the Literature and Current Best Practice Across Six Large United Kingdom Centers[10]
Section 1.2.4 Novel Insights in the Management of Vernal Keratoconjunctivitis (VKC): European Expert Consensus Using a Modified Nominal Group Technique 2023[11]
Management of vernal keratoconjunctivitis in children in Saudi Arabia. Oman J Ophthalmol. 2020;13(1):3-12. Published 2020 Feb 17. doi: 10.4103/ojo.OJO_263_2018[12]

1.2.1 Brazilian Guidelines for the Monitoring and Treatment of Pediatric Allergic Conjunctivitis (2021)

The Brazilian guidelines' evidence levels and grades of recommendations are outlined below[9]:

Table 3. The Brazilian Guidelines' Evidence Levels and Grades of Recommendations

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies, or high-quality case-control or cohort studies, with a very low risk of confounding bias
2+	Well-conducted case-control or cohort studies with a low risk of confounding bias
2-	Case-control or cohort studies with a high risk of confounding bias
3	Nonanalytic studies (case reports, case series); 4 Expert opinion.
4	Expert opinion
Grades of recommendations	

A	At least one meta-analysis, systematic review, or RCT rated as 1++, or a systematic review of RCTs, or a body of evidence consisting principally of studies rated as 1+ and demonstrating overall consistency of results.
B	Evidence including studies rated as 2++ and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 1++ or 1
C	Evidence including studies rated as 2+ and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4, or extrapolated evidence from studies rated as 2+.

The Brazilian guidelines' recommendations are assigned the class of recommendations defined in the preceding table:

Diagnosis of AC

- The diagnosis of ocular allergy is based on family and personal history of atopy, symptoms, clinical signs, and, eventually, additional tests.
- Ocular allergy is usually bilateral, with itching, accompanied by tearing and a burning sensation, as the most common symptom. Visual disturbance and photophobia can occur in severe cases.
- A slit-lamp ophthalmological examination may reveal watery or mucoid secretions, eyelid edema, chemosis, papillary hypertrophy in the palpebral conjunctiva, conjunctival hyperemia, limbal nodules, keratitis, and corneal involvement.
- Complementary tests, such as skin tests, and measurement of IgE specific levels in serum or tears can be requested.
- However, skin tests tend to be negative in the absence of an association with rhinitis, and the IgE dosages may not be conclusive, since 24% of patients may be sensitive to multiple allergens. Thus, cytological diagnosis is usually reserved for research purposes.

Treatment of AC

- The initial treatment consists of nonpharmacological measures that aim to prevent or minimize contact between the allergen and the conjunctiva.
- If nonpharmacological measures are insufficient, topical pharmacological treatment is started with antihistamines, mast cell membrane stabilizing agents, multiple-action drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids.

- Systemic allergen-specific immunotherapy can be used to suppress or regulate the immune response. Immunotherapy not only helps to control symptoms but also slows the progression of allergic disease.

Nonpharmacological measures

- Nonpharmacological measures include general environmental measures to reduce exposure to allergens (e.g., elimination of domestic dust, fungi, and pollen) and specific actions, such as the use of cold-water compresses, preservative-free artificial tears, and local cleansing with saline solution to wash the allergens from the conjunctiva and to contract the conjunctival vessels to relieve edema and hyperemia. In addition, sunglasses can be used to prevent contact with suspended allergens and for photophobia relief (grade of recommendation A)

Topical treatment

- First-generation topical eye antihistamines act by blocking receptor H1; however, they are poorly tolerated and have limited effect and potency (grade of recommendation D)

  Their combination with vasoconstrictors extends their therapeutic effect, although at the expense of rebound hyperemia and tachyphylaxis as undesirable common adverse effects. Long-term use of vasoconstrictors is not recommended, and these drugs should be administered with caution to patients with glaucoma, hyperthyroidism, or cardiovascular disease (grade of recommendation D)

- Mast cell membrane stabilizers must be administered every 6 to 8 hours for at least 2 weeks; consequently, adherence to their use is generally low (grade of recommendation A)

- Multiple-acting agents act as mast cell stabilizers, selective H1 receptor antagonists (**olopatadine** and **ketotifen**), and modulators of the anti-inflammatory activity of eosinophils. Some, such as **Epinastine**, act on H1 receptors (reducing itching) and H2 receptors (reducing vasodilation), whereas others, such as **alcaftadine**, also block H4 receptors. Multiple-acting agents have prompt and long-lasting effects and have proven more effective than **fluorometholone** in the treatment of SAC (grade of recommendation A).

- Topical NSAIDs have proven efficacy against hyperemia and conjunctival itching (grade of recommendation A). Ketorolac is approved for the treatment of AC but has been reported to be less effective than **olopatadine** and **emedastine**. The use of topical NSAIDs in children is also limited by their burning sensation.

- Topical ocular corticosteroids are not considered a first-choice therapy for AC, although drugs in lower concentrations (**fluorometholone**, **loteprednol**, and **rimexolone**) can be used to treat moderate inflammation. The drugs of choice for severe inflammation are **dexamethasone** and **prednisolone** (grade of recommendation B).
- Patients with severe allergic keratoconjunctivitis, giant papillae, intense limbic involvement, or recurrent corneal ulcers can be given a supratarsal injection of corticosteroids as an adjuvant treatment option. Satisfactory results can be achieved with injections of 0.4 to 0.5 mL of dexamethasone phosphate (4 mg/mL), prednisolone acetate (40 mg/mL), or triamcinolone acetate (10.5 mg/mL). Repeated injections may be indicated at intervals of approximately 6 months (grade of recommendation D).
- Topical nasal corticosteroids are not considered a treatment of choice for AC, but they can improve ocular symptoms by reducing the nasal-ocular reflex in patients with rhinoconjunctivitis. In particular**, mometasone furoate, fluticasone furoate**, and **fluticasone plus azelastine furoate** can alleviate the symptoms of allergic rhinoconjunctivitis (grade of recommendation A). Regarding the effectiveness in controlling ocular symptoms in patients with allergic rhinoconjunctivitis, no superiority has yet been established between intranasal corticosteroids and oral antihistamines.
- Immunomodulatory eye drops (cyclosporin and tacrolimus) are expected to have equivalent or better effects for long-term control than steroid eye drops and to spare their use.

Systemic treatment

- First-generation H1 antihistamines are not recommended, because of their sedative effect and anti-cholinergic activity. Second-generation drugs (desloratadine, ebastine, loratadine, and rupatadine) have similar efficacy but a more manageable sedation profile and fewer adverse effects (grade of recommendation B).

Immunotherapy

- Specific immunotherapy improves ocular symptoms in patients with allergic rhinoconjunctivitis even after discontinuation of treatment. The conjunctival sensitivity threshold to the allergen increases from before to after immunotherapy, and the treatment also produces a 63% reduction in the need for medication in patients with rhinoconjunctivitis or SAC, but not in patients with PAC (grade of recommendation A).

- The decision to start treatment depends on several factors: severity of the allergic disease, response to environmental prevention measures, patient acceptance, and adherence to treatment.

Systemic immunosuppression

- Immunomodulators may be an option for severe cases that are refractory to topical treatment to avoid systemic corticosteroid use and its inherent adverse effects.
- Both tacrolimus and cyclosporin act by inhibiting calcineurin (a calcium-dependent phosphatase), which activates the nuclear factor and causes proliferation and activation of T cells.
- The use of T lymphocyte signal transduction inhibitors in the treatment of AKC in patients who are refractory to conventional therapy or other immunomodulatory therapy was shown to be effective in sparing the use of corticosteroids.

Monoclonal antibodies

- The humanized anti-IgE monoclonal antibody **omalizumab**, which is indicated for the treatment of asthma and chronic urticaria, has also been shown to have an effect, although incomplete, on the control of severe VKC
- The anti-IL-4 medication dupilumab, which is indicated for atopic dermatitis, severe asthma, and chronic rhinosinusitis, might also be useful as an AC treatment, considering its mechanism of action.

Surgical treatment

- Surgical intervention is reserved for patients with severe vision-threatening disease, characterized by the presence of large cobblestone papillae, active shield ulcers, limbic stem cell deficiency with extensive conjunctivalization, and extensive corneal scarring.
- These patients are usually refractory to pharmacological therapy and need close monitoring for complications, such as infection, permanent corneal opacity, cataracts, and glaucoma.

Table 4 summarizes the topical treatment options for allergic conjunctivitis:

Table 4. Medication Class, Mechanisms of Action, Side Effects, and Dosage of Topical Treatment of Allergic Conjunctivitis

Classification	Mechanism of action	Side effects	Topical ophthalmic agents generic name	Dosage
Artificial tears	Dilution and removal of antigens from the eye surface	Chronic use can lead to chemical conjunctivitis due to preservative exposure	Cellulose derivative	• With preservatives: 1 drop up to 6 times daily • Preservative free: unlimited use
Topical decongestants	Vasoconstriction via stimulation of alpha-adenoreceptors	Chemical conjunctivitis, follicular reaction, rebound hyperemia, pupillary dilation; contraindicated in patients with narrow-angle glaucoma	Emedastine, ephedrine, naphazoline, pheniramine	1 or 2 drops up to 4 times daily
Topical antihistamines	Relatively selective histamine receptor antagonist	Ocular burning, headache, bitter taste	Azelastine, levocabastine	1 or 2 drops up to 4 times daily
Mast cell stabilizers	Mast cell degranulation blockage, stabilizing the cell and preventing the release of histamine and related mediators	Ocular burning, stinging and itching sensations	Sodium chromoglycate, lodoxamide tromethamine, nedocromil	1 or 2 drops twice up to 4 times daily
Multiple-action agents	Selective H1-receptor antagonists and mast cell stabilizers	Itching, irritation, burning, stinging sensations, eye redness	Olopatadine, alcaftadine, ketotifen	1 drop once daily 1 drop up to 3 times daily
NSAIDs	Cyclooxygenase and prostaglandins blockage	Ocular burning, stinging, and itching sensations	Ketorolac tromethamine, diclofenac, nevanac	1 drop up to 6 times daily
Corticosteroids	Interfere with intracellular protein synthesis and cause blockage of phospholipase A2, the enzyme responsible for the formation of arachidonic acid	Intraocular pressure increase, cataracts	Loteprednol, prednisolone, fluormetolone, dexametasone	2/2 hs-4/4 hs for 3-4 weeks Taper when using for more than 7 days
Immunosuppressors	Anti-inflammatory/immunomodulatory activity by inhibiting the activation of NF-kB, a nuclear factor involved in regulation of immune and proinflammatory cytokine genes	Eye burning, headache, foreign body sensation, conjunctival hyperemia	Cyclosporin	1%-2%: 2-4 times daily 0.05%: 2-4 times daily
			Tacrolimus	Ointment 0.02%-0.03% Drops 0.03%-0.1% 2-4 times daily

NF-kB= nuclear factor kB; NSAIDS= nonsteroidal anti-inflammatory drugs.

Retrieved from Ronconi CS, Issaho DC, Ejzenbaum F, et al. Brazilian guidelines for the monitoring and treatment of pediatric allergic conjunctivitis. Arq Bras Oftalmol. 2021;85(4):415-425. doi:10.5935/0004-2749.20220053.

Disease control criteria

- The guidelines for managing allergic conjunctivitis (AC) rely on control criteria proposed by the Document on AC (DECA). These criteria involve assessing ocular symptoms within two weeks of evaluation, using the Visual Analog Scale (VAS) score, and conducting an ophthalmological examination, particularly focusing on conjunctival hyperemia graded by the Efron scale.
- Control of AC is determined by the absence of symptoms or the presence of symptoms that are not uncomfortable and occur no more than two days a week. Conversely, uncontrolled AC is characterized by ocular symptoms present for more than two days a week or worsening in frequency and severity.
- The VAS score, which patients use to rate the severity of their symptoms on a scale from 0 to 10, is a valuable tool for assessing control. AC is considered controlled when the VAS score is below 5.

- In the ophthalmological examination, control is determined by the degree of conjunctival hyperemia. AC is considered controlled if hyperemia is rated as 0 or 1 on the Efron scale.
- Clinical control criteria of allergic conjunctivitis are summarized in table 5:

Table 5. Clinical Control Criteria of Allergic Conjunctivitis

Symptoms	Controlled (all criteria below)	Uncontrolled (at least 1 of the following)
Itchiness Tearing Visual discomfort	No symptoms or symptoms < 2 days/week	Any intensity if present > 2 days/week
Visual Analog Scale	< 5	≥ 5
Hyperemia (Efron scale)	0-1	2-4

Adapted from Ronconi CS, Issaho DC, Ejzenbaum F, et al. Brazilian guidelines for the monitoring and treatment of pediatric allergic conjunctivitis. Arq Bras Oftalmol. 2021;85(4):415-425. doi:10.5935/0004-2749.20220053.

Clinical monitoring

Ophthalmological assessments to assess AC control should be performed as follows:

Mild Cases - reassess every 4 weeks and maintain treatment until symptoms are resolved.

Intermittent and Perennial Moderate Cases - reassess every 4 weeks.

➔ Controlled: maintain treatment for 4 weeks and consider tapering the eye drops.

➔ Uncontrolled: treat as a severe case.

OBS1 (observation): Consider using mild corticosteroids in cases of initial corneal involvement.

OBS2: Consider specific immunotherapy in persistent cases or when associated with other manifestations of allergy.

Severe Cases - reassess every 2 weeks.

➔ Controlled: taper corticosteroid drops every 3 days.

➔ Uncontrolled: reconsider the diagnosis.

OBS1: Consider specific immunotherapy in persistent cases or when associated with other manifestations of allergy.

OBS2: Consider therapy with biologicals.

Table 6 shows the applicability of treatment modalities for allergic conjunctivitis according to its severity (grade of recommendation D)

Table 6. The Applicability of Treatment Modalities for Allergic Conjunctivitis According to its Severity

Classification	Mild	Intermittent moderate	Perennial moderate	Severe	Vision-threatening conditions
Nonpharmacologic measures	x	x	x	x	x
Artificial tears	x	x	x	x	x
Topical decongestants	x	x	x	x	x
NSAIDs	x				
Selective H1-receptor antagonists and mast cell stabilizers	x	x	x	x	x
Mild corticosteroids		x	x		
Cyclosporin			x		
Corticosteroids		Only if corneal involvement	Only if corneal involvement	x	x
Tacrolimus				x	x
Supratarsal corticosteroids					x
Papillae excision					x
Ulcer debridement					x
Immunotherapy			x*	x*	x*
Monoclonal antibodies				x**	x**
Oral antihistamines/antileukotrienes		x	x	x	x
Nasal corticosteroids		x***	x***	x***	x***

NSAIDS= nonsteroidal anti-inflammatory drugs.
* Consider specific immunotherapy in persistent cases or when associated with other allergies.
** Consider monoclonal antibody therapy.
*** When associated with nasal symptoms.

Retrieved from Ronconi CS, Issaho DC, Ejzenbaum F, et al. Brazilian guidelines for the monitoring and treatment of pediatric allergic conjunctivitis. Arq Bras Oftalmol. 2021;85(4):415-425. doi:10.5935/0004-2749.20220053.

1.2.2 Japanese Guidelines for Allergic Conjunctival Diseases (2020)

The main recommendations (ungraded) published in 2020 by the Japanese Society of Allergology are summarized below[2].

Prophylaxis: self-care

- Avoidance and elimination methods by types of antigens

Perennial avoidance and elimination of antigens can be achieved by arranging the patient's daily living environment, especially their indoor environment. In contrast, the avoidance of pollen antigens is conducted mainly during the pollen-flying period.

- Self-care for allergic conjunctivitis
    - *Effect of glasses for prevention of pollens*

During pollen-flying period, goggle-type glasses are recommended to carry out daily activities such as riding a bicycle and having a stroll with a dog, although even glasses themselves can reduce the amount of pollen flying into the ocular surface.

- *Contact lens wear*

During the pollen-flying period, avoidance of contact lens wear and changing to glasses is advised to avoid antigens.

- *Eye washing by artificial tears*

Artificial tears or eye wash solutions without preservatives are useful to wash antigens out of the ocular surface to reduce allergic symptoms. Allergens or dust should not touch the eye surface when washing the surrounding skin. Frequent eye washing with tap water should be avoided because it reduces the tear layer stability.

Treatment: Medical Care

➢ Fundamentals of treatment

Drug treatment is the preferred treatment for ACDs. The first option is antiallergic eye drops, which are the basic treatment for allergic conjunctivitis, followed by the differential use of steroid eye drops as necessary according to the severity. For severe ACDs (AKC and VKC), additional use of immunosuppressive eye drops, steroid oral medicines, sub-tarsal conjunctival steroid injection, and surgical treatment such as papillary resection should be considered.

Available antiallergic eye drops are listed in table 7:

Table 7. Antiallergic Eye Drops

Class	Generic Name
Mediator antireleasers	Disodium cromoglicate
	Pemirolast potassium
	Tranilast
	Ibudilast
	Acitazanolast hydrate
Histamine H1 receptor antagonists	Ketotifen fumarate
	Levocabastine hydrochloride
	Olopatadine hydrochloride
	Epinastine hydrochloride

Adapted from Miyazaki D, Takamura E, Uchio E, et al. Japanese guidelines for allergic conjunctival diseases 2020. Allergology International. 2020;69(3):346-355. doi:10.1016/j.alit.2020.03.005.

Steroids

1. Eye drops

When a sufficient effect cannot be obtained by antiallergic eye drops only, steroid eye drops with a titer corresponding to the severity of inflammation are combined. It is necessary to measure the intraocular pressure regularly in children because the incidence of elevated intraocular pressure is high. The steroid eye drops are summarized in table 8:

Table 8. Steroid Eye Drops

Generic names	Concentration (%)					
	0.01	0.02	0.05	0.1	0.25	0.5
Betamethasone sodium phosphate	X			X		
Dexamethasone sodium phosphate				X		
Dexamethasone sodium metasulfobenzoate		X	X	X		
Fluorometholone		X	X	X		
Hydrocortisone acetate						X

Adapted from Miyazaki D, Takamura E, Uchio E, et al. Japanese guidelines for allergic conjunctival diseases 2020. Allergology International. 2020;69(3):346-355. doi:10.1016/j.alit.2020.03.005.

2. Oral medicines

Medicines are used for pediatric and other patients for whom sub-tarsal conjunctival injection is difficult and for patients with corneal epithelial defect. The standard administration period is 1-2 weeks in consideration of its side effects. It is necessary to treat patients with caution for its systemic side effects in cooperation with internists and pediatricians.

3. Eye ointments

When a sufficient effect is not obtained by antiallergic eye drops only or steroid eye drops cannot be used, ointments are used. Ointments can be applied before going to sleep to realize the effect while sleeping. The same cautions as those in using steroid eye drops are necessary. The steroid eye ointments are summarized in table 9:

Table 9. Steroid Eye Ointments

Generic names	Concentration (%)				
	0.01	0.02	0.05	0.1	0.25
Compounding agent of betamethasone phosphate and fradiomycin sulfate				X	
Dexamethasone sodium metasulfobenzoate			X		
Compounding agent of methylprednisolone and fradiomycin sulfate				X	
Prednisolone					X

Adapted from Miyazaki D, Takamura E, Uchio E, et al. Japanese guidelines for allergic conjunctival diseases 2020. Allergology International. 2020;69(3):346-355. doi:10.1016/j.alit.2020.03.005.

4. Sub-tarsal conjunctival injection of steroid suspension

Triamcinolone acetonide or **betamethasone** suspension is injected to the sub-tarsal conjunctiva of the upper eyelid in intractable or severe cases. With caution for the elevation of intraocular pressure, it is desirable to avoid repeated use or the application to children aged <10 years.

Immunosuppressive eye drops

At present, 2 kinds of immunosuppressive eye drops (**cyclosporine** and **tacrolimus**) have been approved as treatment drugs for VKC. Immunosuppressive eye drops are expected to have equivalent or better effects than steroid eye drops. Cyclosporine enables the gradual reduction of the doses of steroid eye drops by combined administration with antiallergic eye drops and steroid eye drops. Tacrolimus itself also has effects on steroid-resistant severe cases.

Surgical treatment

For cases where symptoms are not alleviated by drug treatment and conjunctival papillary hyperplasia progresses to cause worsened corneal epithelium disorder, a tarsal conjunctival resection, including the papillae may be performed. While the treatment effect is immediate, it may recur in some cases. Although corneal plaques may be removed by surgical curettage, the treatment is performed only when the pathologic condition has been alleviated.

Selection of treatment methods

- *Allergic conjunctivitis*

The first option is antiallergic eye drops. A mast cell stabilizer can be combined with a histamine H1 receptor antagonist. During a period with severe symptoms, steroid

eye drops are additionally administered. In SAC, administration of an antiallergic eye drops is started around 2 weeks prior to the predicted day of the start of flying pollen or at the time when few symptoms appear so that the symptoms decrease during the peak time of flying pollen.

- *Vernal keratoconjunctivitis*

For moderate or more severe cases such those for which antiallergic eye drops alone are not sufficiently effective, immunosuppressive eye drops are additionally administered.

When improvement cannot be achieved, addition of steroid eye drops or switching to tacrolimus eye drops is recommended. Depending on the severity of the symptoms, a steroid oral medicine and subtarsal conjunctival steroid injection or surgical treatment should be considered. When the symptoms are alleviated, the dose of steroid eye drops, or the number of instillations should be gradually decreased. After remission is attained, antiallergic eye drops with or without immunosuppressive eye drops can be used for long-term control.

Introductory points for medical specialists

- For a case of conjunctivitis presenting with ocular itching as the major symptom, anti-allergic ophthalmic eye drops can be prescribed. However, in cases where symptoms are not alleviated after 1-2 weeks of treatment, it is advisable for the physician to recommend the patient to visit an ophthalmology department considering differential diagnosis of a bacterial or viral infection.
- When the therapeutic effects are insufficient, steroid eye drops are administered in combination. However, continued use of steroid eye drops may cause increased intraocular pressure or exacerbation of ocular infections; hence, regular examinations by an ophthalmologist are required.
- Contact lens wear may aggravate symptoms such as ocular itching, hyperemia, and ocular discharge, and may often need to be discontinued prior to treatment under consultation with a family ophthalmologist.
- Prescription of immunosuppressive eye drops requires management by ophthalmologist; therefore, refractory pediatric patients with suspected VKC or AKC should be recommended to be examined in an ophthalmology department.

1.2.3 Management of Vernal Keratoconjunctivitis in Children in the United Kingdom: A Review of the Literature and Current Best Practice Across Six Large United Kingdom Centers (2023)

Based on discussions between experienced clinicians from six large centers across the United Kingdom (UK), this review article describes best practice recommendations for UK settings, including principles for diagnosis, referral, initial and long-term management, and supportive care. Recommendations include guidance on referral timing, which should depend on vernal keratoconjunctivitis (VKC) severity, and a stepwise approach to treatment[10].

Symptoms and Diagnosis

- Taking a thorough history is an essential step in identifying VKC.
- Symptoms of VKC generally worsen in the spring and summer.
- Seasonality of the child's disease is therefore useful to establish seasonal VKC, although it must be borne in mind that advanced VKC can be perennial: a lack of seasonality is insufficient to rule it out.
- House dust mite allergy may be a significant triggering factor at other times of the year, and nonspecific stimuli such as sun and wind can also worsen symptoms.
- Characteristic symptoms experienced by children with VKC include itching with redness of the eye, present in more than 90% of patients with VKC: If itching is not present, another non-allergic ocular disorder must be considered. Photophobia may indicate corneal involvement.
- The differential diagnosis includes atopic keratoconjunctivitis, with certain key differences between the two. Notably, atopic keratoconjunctivitis generally affects adults, but can also affect children.
- It is characterized by severe allergic eye disease principally associated with atopic dermatitis of the eyelids.

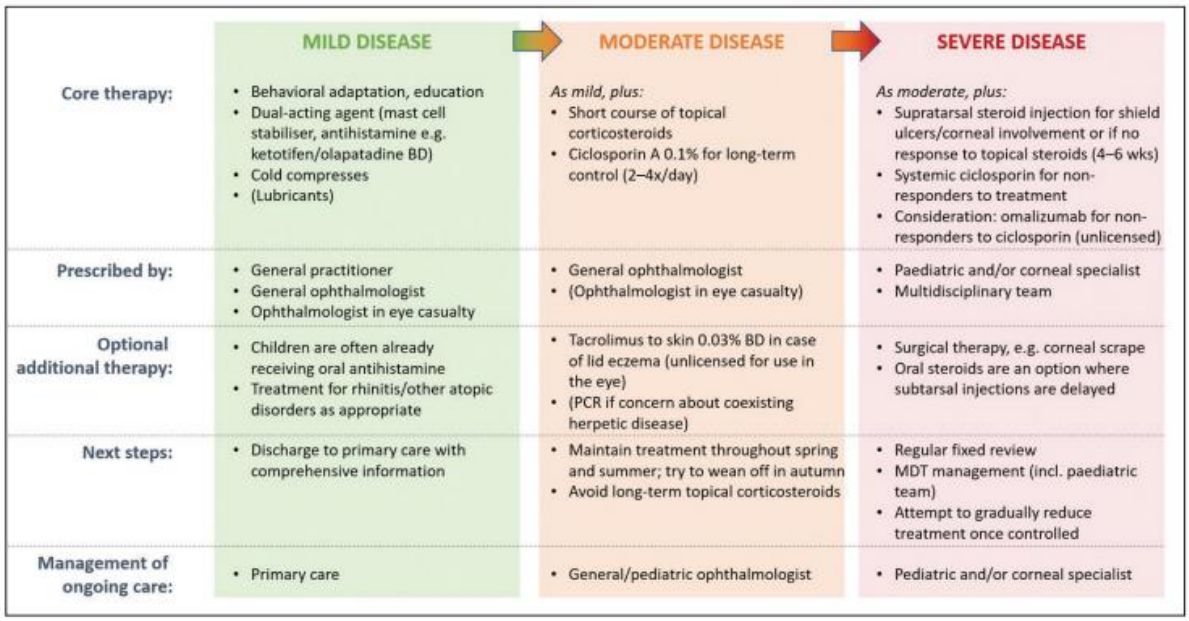
Severity

- VKC can be classified as mild, moderate, or severe. This classification is important to determine the next steps for the patient.

Initial Treatment

- **Mild:** Children who have not previously been treated for VKC, with no sight-threatening signs and a low impact on quality of life, can be classified as having mild disease and treated with behavioral adaptation and largely topical therapy.
    - Preservative-free artificial tear eye drops (lubricants) can play a role as adjuncts in the treatment of VKC, by diluting tear cytokines and providing symptomatic relief.
    - Of note, preservatives in topical therapies may damage the ocular surface, as well as causing itching and intolerance. Wherever possible, preservative-free formulations should be used for all topical treatments discussed.
- **Moderate:** The mainstay of initial treatment for moderate disease is topical corticosteroid therapy, the choice of which can be partly guided by findings of limbitis and/or cobblestones.
    - Steroid-sparing agents such as 0.1% cyclosporine A should be considered if inflammation cannot be controlled sustainably with dual-acting agents only.
    - For patient's refractory to cyclosporine A, topical tacrolimus is an optional alternative. Both 0.03% and 0.1% preparations are available including an ointment for atopic dermatitis of the eyelids.
- **Severe:** In addition to the treatments for moderate VKC, treatment options for severe VKC include high-frequency and high-concentration topical steroids.
    - Pulsed oral (e.g., prednisolone 1 mg/kg for 3 days to a maximum of 40 mg daily) and injected supratarsal (e.g., triamcinolone acetonide 20 mg) corticosteroids are reserved for those not responsive to potent topical steroids.
    - Shield ulcers include an epithelial defect and may require prophylactic topical antibiotics (e.g., chloramphenicol 0.5%, preservative free) and intensive corticosteroids. If there is an infiltrate associated with a shield ulcer, a topical quinolone or equivalent broad-spectrum antibiotic (preservative-free) should be used for at least 48 hours and reviewed before initiating *topical corticosteroids* or *cyclosporine A*.
    - Supratarsal steroid injections can be given concurrently if the patient has surgery.

Figure 1 summarizes the recommended management approaches for mild, moderate, and severe disease.



	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)	*As mild, plus:* • Short course of topical corticosteroids • Ciclosporin A 0.1% for long-term control (2–4x/day)	*As moderate, plus:* • 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 1. *Summary of recommended management approaches for mild, moderate, and severe vernal Keratoconjunctivitis*

Retrieved from Ghauri AJ, Biswas S, Manzouri B, et al. Management of Vernal Keratoconjunctivitis in Children in the United Kingdom: A Review of the Literature and Current Best Practice Across Six Large United Kingdom Centers. J Pediatr Ophthalmol Strabismus. 2023;60(1):6-17. doi:10.3928/01913913-20220328-01

Long-term Management

Controlling Flare-ups

Families need to be aware that exacerbations can occur even with effective treatment. They should be aware of the need for rapid access to the eye clinic in this case. If more than one flare-up occurs within the same 12-week period despite good treatment adherence, treatment should be stepped up.

Long-term Management and Follow-up

- Duration and frequency of hospital follow-up depends on the severity and type of treatment. The ideal pathway is an initial follow-up appointment approximately 2 to 4 weeks after treatment initiation, or earlier in the case of sight-threatening complications (1 to 2 weeks). If the patient has been prescribed steroids, follow-up every 6 weeks is recommended. Topical steroids are typically prescribed by the hospital eye clinic for 4 to 6 weeks; the prescription can only be extended by the general practitioner under explicit guidance by the hospital team specifying the intended treatment frequency

and duration. Follow-up after initiating topical cyclosporine A should take place at approximately 3 months.

- Long-term use of cyclosporine A has been found to be well tolerated, but topical steroid use over an extended period should be carefully monitored to avoid sight-threatening complications such as glaucoma and cataract.
- Follow-up for stable patients is recommended every 6 to 12 months; for patients with seasonal symptoms, appointments should ideally be scheduled based on the pattern of previously observed exacerbations or arranged via patient-initiated follow-up. If a patient has been asymptomatic for 1 year, treatments can be stepped down and tapered. In many cases, the severity of VKC will reduce after puberty. Discharge to primary care can be considered if there is no need for ongoing steroids or topical cyclosporine A.

Quality of Life

- Assessment of quality of life is an important part of patient follow-up and should occur at the first consultation and then at least annually.

Supportive Care

- Many children with VKC have many comorbidities and the disease itself is prone to exacerbations and flare-ups that are difficult to anticipate and control, potentially becoming a source of family conflict.

1.2.4 Novel Insights in the Management of Vernal Keratoconjunctivitis (VKC): European Expert Consensus Using a Modified Nominal Group Technique (2023)

The EUR-VKC Group provides recommendations on the assessment, diagnosis, management, referral, and follow-up of patients with VKC. Evidence levels and grades of recommendations are outlined in table 10[11]:

Table 10. EUR-VKC Evidence Levels and grades of Recommendations

For each recommendation, the value of the votes was averaged, and the strength of the recommendation determined. Recommendations herein are presented with certainty and strength.	
Average scores ≥ 1.6	Very strong (+++)
≥ 1.1 to <1.6	Strong (++)
≥ 0.7 to <1.1	Moderate (+)

Only recommendations on which C 75.0% of members agreed (consistent with other consensus programmes and nominal group techniques), as predetermined by the EUR-VKC Group, are included as reaching consensus.

The European Expert Consensus's recommendations are assigned the class of recommendations defined in the preceding table:

- ➔ The aim of this European expert panel (the EUR-VKC Group) was to amalgamate expert opinion and the latest evidence to achieve consensus on the management of VKC – to optimize care and improve the quality of life of children with VKC.
- ➔ The experts agreed that VKC can be classified as mild, moderate, or severe, and should be managed according to severity in a stepwise manner, with treatment intensity escalating as the disease severity increases.
- ➔ Timely diagnosis and treatment initiation appropriate to the severity of VKC are crucial to prevent sight loss and improve the quality of life of children with VKC.

Staged Assessment of VKC

- The EUR-VKC Group has reached a consensus on the significance of having both primary care physicians and general ophthalmologists evaluate the clinical and family history of allergies or atopic conditions, such as eczema, asthma, and rhinitis. This assessment is crucial because the presence of ocular allergies may necessitate additional examination for differential diagnosis. Furthermore, it's important to consider potential external and environmental factors that could trigger or worsen symptoms in patients suspected of having VKC. Additionally, the group stressed the importance of understanding how VKC affects the patient's quality of life, as well as the duration and seasonality of the disease.
- The group distinguished common signs and symptoms of VKC of which different specialties should be aware as shown in the figure below:

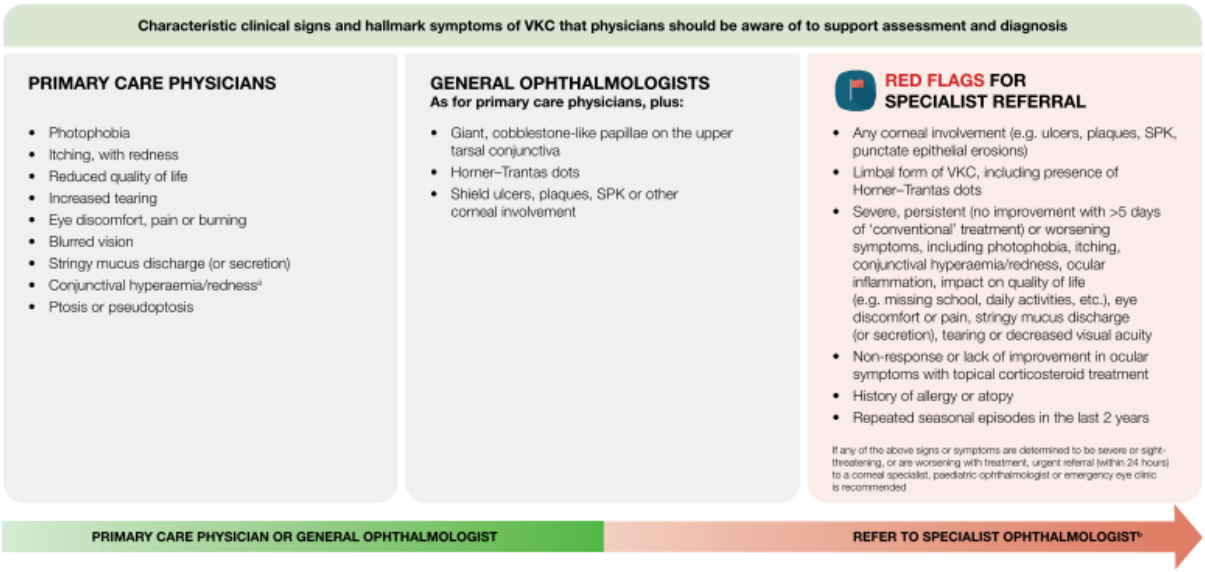


Figure 2. *Clinical signs and hallmark symptoms for the assessment and diagnosis of VKC.*

[a] If redness or 'watery' eyes are observed in isolation, referral may only be appropriate if there is no improvement in signs and symptoms following 1–2 weeks of conventional treatment (defined as typical first-line pharmacological therapy, including antihistamines, mast cell stabilizers or dual-acting agents).

[b] Unless the general ophthalmologist is experienced and competent in the management of VKC. SPK superficial punctate keratitis, VKC vernal keratoconjunctivitis

Retrieved from Dahlmann-Noor A, Bonini S, Bremond-Gignac D, et al. Novel Insights in the Management of Vernal Keratoconjunctivitis (VKC): European Expert Consensus Using a Modified Nominal Group Technique. Ophthalmol Ther. 2023;12(2):1207-1222. doi:10.1007/s40123-023-00665-5.

Stepwise Management Approach Based on Severity and Progression of VKC

- The EUR-VKC Group reached a consensus that it is essential to consistently offer patients and their family or caregivers both support and education. This education should prioritize strategies for avoiding triggers or factors that worsen symptoms, as well as allergens. It should also include guidance on maintaining lid hygiene and the proper utilization of cold compresses and ocular lubricants or artificial tears. It's important to note that these lubricants should be preservative-free, as preservatives can potentially induce allergies or harm the corneal surface.
- As first-line pharmacological therapy, dual-acting agents (e.g., olopatadine, azelastine hydrochloride, epinastine, ketotifen) may be considered rather than monotherapy with antihistamines or mast cell stabilizers (e.g., sodium

cromoglycate, nedocromil, lodoxamide), depending on formulary, local recommendations, and availability.

- Short-pulse *topical* corticosteroids are effective to tackle inflammation and manage acute exacerbations or when the cornea is involved and should be considered for patients with moderate-to-severe disease either alone, as an add-on to topical CsA, or as rescue therapy under the supervision of an ophthalmologist, and repeat cycles avoided, where possible, to prevent dependency.
- The long-term use of corticosteroids is associated with an increased risk of adverse events including elevated intraocular pressure and glaucoma, formation of cataracts, delayed wound healing and increased susceptibility to infection. Notably, corticosteroid-induced glaucoma is a debilitating disease that may cause irreversible loss of vision and potentially blindness.
- The use of high-frequency or oral corticosteroids (in short pulses) may be appropriate for patients with persistent corneal complications or non-response to prior treatments but should only be prescribed by a clinician experienced in the use of these medications.
    - Measuring IOP before starting treatment allows the physician to monitor changes over time and identify any potential steroid-induced complications. Some 'soft' corticosteroids (e.g., loteprednol, hydrocortisone) may not completely resolve VKC exacerbations, and longterm treatment can lead to corticosteroid dependency.
    - 'High-potency' topical corticosteroids (e.g., dexamethasone), used as a pulse therapy for 3–5 days without tapering, could be more efficacious in resolving exacerbations and less likely to increase IOP than the longer-term use of 'soft' corticosteroids.
- Topical immunomodulators, such as CsA (Ciclosporin A), should be taken into consideration for patients dealing with moderate to severe or persistent VKC. Additionally, individuals with a dependency on corticosteroids may also benefit from them to maintain long-term control. When short-term corticosteroid treatments are frequently employed for a duration of three months or more, it is advisable to explore the use of topical CsA for sustained symptom management. It's worth noting that topical CsA has demonstrated a significant reduction in the need for corticosteroids, potentially allowing for symptom control without the use of corticosteroids. However, it may not be suitable for patients with moderate VKC who lack other indications of disease progression or a risk of recurrence.
- Oral antihistamines may be used as **adjunctive therapy for mild flare-ups** or in the case of allergic rhinitis, if required.

- Advanced systemic treatments (e.g., immunomodulators, biologics) should only be prescribed in appropriate settings (e.g., patients with recalcitrant disease or involving other allergic manifestations) and by clinicians experienced in their use. Allergen-specific immunotherapy is only recommended where there is clearly defined systemic hypersensitivity to an identified allergen.
- In general, if there is no improvement within 2–4 weeks of treatment and symptoms remain persistent, then the patient should be referred to a specialist ophthalmologist.
- Patients with VKC who may benefit from surgical intervention (e.g., debridement for shield ulcers) should be referred to a corneal specialist or pediatric ophthalmologist, or an emergency eye clinic.

The full list of recommendations regarding the stepwise management of VKC is found in the figure below.

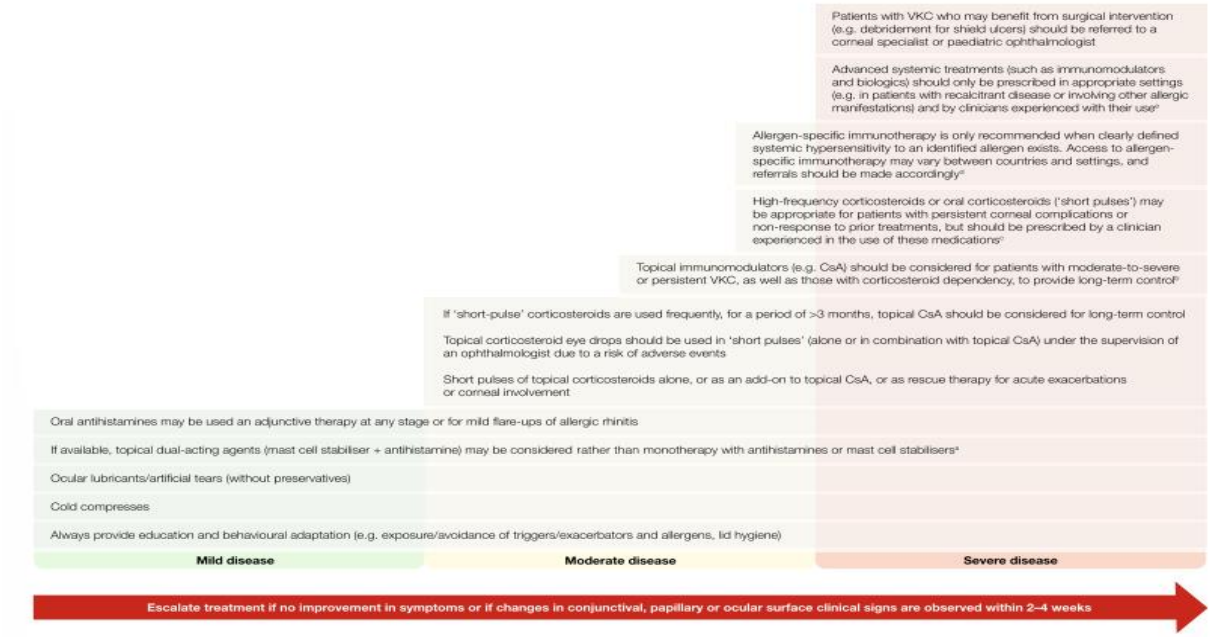


Figure 3. *Stepwise management of mild, moderate, and severe VKC*

[a] If available and depending on formulary and local recommendations.

[b] CsA may not be appropriate for moderate VKC without other signs.

[c] Recommendation revised from round 1 (where two out of seven group members did not agree, and the recommendation was 'Weak'): the use of high-frequency corticosteroids or oral corticosteroids ('short pulses') may be appropriate for patients with persistent corneal complications or non-response to prior treatments but should only be prescribed by a corneal specialist or pediatric ophthalmologist.

[d] Recommendation revised from round 1 (where two out of seven group members did not agree, and the recommendation was 'Weak'): systemic treatment (e.g., with immunomodulators, such as CsA, biologics or antihistamines) should only be considered in patients recalcitrant or with non-response to prior therapy, or who have other allergic manifestations.

[e] Recommendation revised from round 1 (where two out of seven group members did not agree, and the recommendation was 'Weak'): allergen-specific immunotherapy is only recommended when clearly defined systemic hypersensitivity to an identified allergen exists. Patients requiring allergen-specific immunotherapy should be referred to an allergologist or specialist ophthalmologist. CsA ciclosporin A, VKC vernal keratoconjunctivitis.

Retrieved from Dahlmann-Noor A, Bonini S, Bremond-Gignac D, et al. Novel Insights in the Management of Vernal Keratoconjunctivitis (VKC): European Expert Consensus Using a Modified Nominal Group Technique. Ophthalmol Ther. 2023;12(2):1207-1222. doi:10.1007/s40123-023-00665-5.

Other Treatments for VKC

- Vasoconstrictors and NSAIDs are not recommended for the treatment of VKC as they do not target the specific inflammatory mechanisms associated with VKC. Vasoconstrictors used to address hyperemia should be used with caution and only for short periods of time due to adverse events.
- In addition, products with herbal extracts, such as chamomile-containing eye drops, should be avoided as they may cross-react with allergens (e.g., Artemisia vulgaris).
- Second- and third-generation systemic antihistamines may be preferred over older first-generation antihistamines due to their favorable efficacy/safety profile, pharmacokinetics, and lack of anticholinergic and sedative side effects.

Long-Term Management and Flare-Ups of VKC

- The EUR-VKC Group agreed that for patients with seasonal symptoms, follow-up appointments may be scheduled based on the pattern of previously observed exacerbations or arranged via patient-initiated follow-up with primary care.
- Families and caregivers should be made aware that exacerbations can occur even with effective treatment. They should be aware of the need to access an eye clinic immediately if a flare occurs, and of how to access that clinic.
- If more than one flare-up occurs within 3 months, despite good treatment adherence, therapy should be stepped up and the patient should be referred to a specialist ophthalmologist.

- Oral antihistamines can be used as an adjunctive treatment for mild flare-ups or in the case of allergic rhinitis.
    - Results from the VEKTIS study suggest that topical CsA drops used year-round may reduce the risk of exacerbations during the peak allergy season, and this should be discussed with the patient and their family and prescribed at the clinician's discretion.
    - If a patient has been asymptomatic for approximately 12 months, then treatment de-escalation may be considered. Discharge back to primary care may be considered if there is no need for ongoing corticosteroids or topical CsA.

Key Information to Communicate with Patients and Caregivers on VKC

- VKC is a chronic, recurrent condition that usually improves with age.
- Rubbing itchy eyes can make the condition worse (with advice on a 'no-touch zone')
- Sunlight, wind, salty water, dust, and heat can exacerbate VKC, so the use of sunglasses, hats, visors, and swimming goggles may be considered.
- An air-filtration system in the home may provide relief.
- Common allergens can exacerbate VKC, and frequently washing the hands, face and hair can reduce exposure to these allergens.
- Cold compresses and preservative-free artificial tears can provide symptomatic relief.
- Adherence to treatment is important; it is important to be aware of the risks associated with the long-term use of corticosteroids and to promptly report any adverse events; and how to optimize the use of topical CsA.
    - All the currently available treatments for VKC are palliative and do not extinguish the complex immune process that initiates and propagates the ocular inflammation associated with VKC.
    - Further investigation is required into the feasibility of steroid-sparing regimens in the treatment of VKC, as well as other potential options including combinations with mast cell stabilizers, antihistamines, calcineurin inhibitors and/or oral montelukast.

1.2.5 Review Article: Management of Vernal Keratoconjunctivitis in Children in Saudi Arabia (2020)

This review article on the management of VKC in Saudi children highlights the importance of how the topical management differs between age groups, of doing cycloplegic refraction for each child as the risk of keratoconus and oblique astigmatism is high in these cases, and of using eye lubricants as a therapeutic and preventive tool for the attacks of the disease. Most of the recent effective medications (especially the off-label ones) are not available in Saudi Arabia, such as tacrolimus, and some are only available to be prepared in tertiary center pharmacies as Cyclosporine A with higher concentrations. Findings are summarized below[12]:

Management

- Diagnosis and management of allergic conjunctivitis is usually by pediatric health-care professionals. Unfortunately, VKC is often misdiagnosed, confused with simple allergic conjunctivitis, and undertreated.
- Pediatric doctors and primary health-care providers prescribe antiallergic medication (including topical administration of antihistamine, mast cell inhibitors, or combinations of both) safely to patients presenting with itching and redness.
    - They should refer such cases to ophthalmologists if the children do not improve in 1 week after starting the medication. Treatment of VKC needs a good understanding of the disease and its chronic course. The parents should be educated about the importance of good compliance with medications and the chronic nature of the disease.

Nonpharmacological Management

- VKC is a type of allergic conjunctival disease that results from exposure to an allergen, so the first line of management is removal and avoidance of the allergen that exacerbates the disease.
- Avoidance of specific/nonspecific triggers could prevent severe manifestations of VKC.
- Cool compresses are useful to reduce the symptoms of itching.

Artificial tears

- Topical lubrication with artificial tears is important as a long-term management of VKC patients, during both active and inactive phases. First, it can reduce the symptoms of itching by a cooling effect.

- During an acute attack and active VKC, it can wash out the inflammatory mediators present in the tear and by this, reduce inflammation.
- Dry eye is a common complication of VKC secondary to limbal stem cell deficiency (LSCD) and tear film instability because of cytological changes in both corneal and conjunctival epithelium. In these cases, lubrication with the use of eye drops in the daytime and eye ointment at bedtime is important.

Pharmacological Management

- The focus of the medical management of VKC is to relieve the debilitating symptoms, reduce the signs, and prevent complications.
- The topical eye drops to treat VKC that are approved by the US Food and Drug Administration (FDA) and Saudi FDA, and given at King Khaled Eye Specialist Hospital, are shown in table 11 and the topical medication for the treatment of vernal keratoconjunctivitis in table 12.

Table 11. Topical Medications for the Treatment of Vernal Keratoconjunctivitis

Medication	Category	Saudi FDA	U.S FDA	KKESH
Levocabastine	Histamine H_1 antagonist	Yes LIVOSTIN 0.05%	Yes LIVOSTIN 0.05%	NF
Emedastine	Selective, histamine H_1 antagonist	Yes EMADINE 0.05%	Yes EMADINE®	NF
Sodium cromoglycate		NF	NF	NF
Iodoxamide	Mast cell stabilizer	NF	Yes ALOMIDE®	NF
Nedocromil sodium 2%	Mast cell stabilizer	NF	ALOCRIL®	NF
Olopatadine	Selective H_1 receptor antagonist and inhibitor of histamine release from the mast cell	Yes Olopat/pataday	Yes Patanol/pataday	Yes Pataday
Epinastine	Histamine H_1 antagonist	Yes RELESTAT 0.05%	Yes ELESTAT®	Yes RELESTAT 0.05%
Naphazoline hydrochloride 0.025% + Pheniramine maleate 0.3%	Redness reliever + antihistamine	Yes Naphcon-A	Yes Naphcon-A	Yes Naphcon-A
Acetylcysteine 5%-10%	For dry eye	NF	NF	Acetyl cysteine topical 10%, 20%
Prednisolone	Corticosteroids	Yes	Yes	Econopred 1% (alcon)
Fluorometholone	Corticosteroids	FML/optilone/flucon	FML	Optilone
Dexamethasone	Corticosteroids			
Loteprednol	Corticosteroids	NF	Yes Lotemax	Yes Lotemax
Cyclosporine A	Immunosuppressant	RESTASIS 0.05%	RESTASIS 0.05%	RESTASIS 0.05%/cyclosporine 1%, 0.1%
Tacrolimus	Immunosuppressant	NF	NF	NF

NF: Nonformulary, KKESH: King Khalid Eye Specialist Hospital, FDA: Food and Drug Administration, FML: Fluorometholone

Retrieved from AlHarkan D. Management of vernal keratoconjunctivitis in children in Saudi Arabia. Oman J Ophthalmol. 2020;13(1):3. doi:10.4103/ojo.OJO_263_2018.

Table 12. Classes of Topical Medication Used for the Treatment of Vernal Keratoconjunctivitis

Class	Drug	Indication	Dose	Comment
Vasoconstrictor/antihistamine combinations	Naphazoline/pheniramine	Rapid onset of action Episodic itching and redness	≥6 years, QID	Short duration of action Tachyphylaxis Mydriasis Ocular irritation Hypersensitivity Hypertension Potential for inappropriate patient use Safety is not established for children <6 years old
Antihistamines	Levocabastine	Relief of itching	≥5 years, BID–QID	Short duration of action<5 years old: Safety and efficacy not established Frequently does not provide complete disease control when used alone
	Emedastine	Relief of signs and symptoms	≥3 years, QID	<3 years old: Safety and efficacy not established
Mast cell stabilizers	Sodium cromoglicate	Relief of signs and symptoms	≥4 years, QID	<4 years: Safety and efficacy not established Long-term usage (not for acute symptoms) Slow onset of action (up to 6 weeks) may be required Prophylactic dosing Frequently does not provide complete disease control when used alone
	Nedocromil	Relief of signs and symptoms	≥3 years, BID	<3 years: Safety and efficacy not established
	Lodoxamide	Relief of signs and symptoms	≥2 years, QID	<2 years: Safety and efficacy not established
Antihistamine/mast cell stabilizers (dual-acting)	Epinastine	Relief of itching	>2 years, BID	<2 years: Safety and efficacy not established No reported serious side-effects
	Ketotifen	Relief of signs and symptoms (especially itching, hyperemia, photophobia, tearing, and hyperemia)	≥3 years, BID	<3 years: Safety and efficacy not established
	Olopatadine	Best used for prevention of the attack	≥2 years: 0.2% (Pataday), QD ≥3 years: 0.1% (Patanol), BID	<2 years (Pataday) or<3 years (Patanol): Safety and efficacy not established
Corticosteroids	Loteprednol* Fluorometholone* Rimexolone* Dexamethasone Prednisolone	Treatment of allergic inflammation Use for moderate to severe forms Relief of signs and symptoms (papillary hypertrophy, Trantas dots, hyperemia, and tearing) *Soft steroids: less risk of increasing intraocular pressure	Used for short term only (high-dose pulse therapy)	Risk for long-term side-effects No mast cell stabilization Potential for inappropriate patient use Requires close monitoring Avoid it if corneal epithelium is compromised
Immunomodulators	Cyclosporine 0.05% (Restasis; single-use or multi-dose vials) Can be prepared commercially (0.1%, 0.5%, 1%, and 2%)	Recommended rather than corticosteroids if corneal epithelium is compromised and in steroids responders Long-term use is considered safe Significant relief of signs and symptoms (itching, Trantas dots, hyperemia and tearing)	≥16 years, BID	<16 years: Safety and efficacy not established Slower onset of action (weeks) Severe burning sensation Risk of relapse if medication is stopped For moderate to severe cases a higher concentration is needed
	Tacrolimus (0.03% - 0.1%)	Effective for cases refractory to cyclosporine Can be used as single medication Significant relief of signs and symptoms (itching, papillary hypertrophy, Trantas dots, hyperemia, and tearing)	*<2 years: Safety and efficacy not established *2–15 years only 0.03% can be used *>15 years, 0.03% or 0.1% can be used (*) Based on dermatology uses of tacrolimus ointment	Severe burning sensation Risk of activation of herpes simplex dendritic keratitis Initial hyperemia (in the first few days of treatment) that subside thereafter Safety of long-term use is not

QID, four times daily; BID, two times daily; OD, once daily

Retrieved from AlHarkan D. Management of vernal keratoconjunctivitis in children in Saudi Arabia. Oman J Ophthalmol. 2020;13(1):3. doi:10.4103/ojo.OJO_263_2018.

Antihistamine

- Second-generation H (1)-antihistamines are among the most prescribed medicines to treat allergic conjunctivitis, including VKC in children.
- *Emedastine* and *Levocabastine* (LEVO), have been reviewed and found to be safe and well tolerated. However, their long-term outcomes and use of standard and uniform parameters to compare the impact are needed.

Mast cell stabilizers

- Sodium cromoglycate: The problem with it is the late starting of its action and lack of immediate relief of the symptoms.
- Lodoxamide: In a meta-analysis of different randomized clinical trials, using different antiallergic medications for VKC patients (LEVO, lodoxamide, nedocromil sodium, mipragoside, N-acetylaspartylglutamic acid, and sodium cromoglycate), lodoxamide was the most effective.

Antihistamine/mast cell stabilizers

- The combination of antihistamine and mast cell stabilizers such as azelastine and olopatadine is safe for children aged 3 years and older.
- Olopatadine: Through its dual action (H (1)-antihistamine/mast cell stabilization effects), olopatadine is superior to sodium cromoglycate.

Olopatadine eye drops are a safe and effective treatment modality, but it is limited in reducing ocular itching.

Steroids

- These are the most potent and effective medications that can be applied as eye drops as well as ointment to treat moderate-to-severe cases of VKC (severe itching with inflamed conjunctiva, presence of limbal infiltrates, corneal involvement, and presence of giant papillae).
- Usually, it is given for a short period to reduce the inflammation in combination with other medications to reduce its dosage and thus minimize the side effects.
- Proper patient and parent counseling is therefore strongly recommended before prescribing steroids to treat VKC. Pulse therapy with topical steroids during disease exacerbations is a common practice. Prednisolone, fluorometholone, and dexamethasone eye drops are prescribed, and with adequate monitoring, this is acceptable. However, loteprednol has the least effect on intraocular pressure (safer than others) and is as effective as prednisolone to treat VKC.

Immunosuppressive eye drops

- *Cyclosporine A (CsA),* It is a nonsteroidal immune modulator and is most effective in treating VKC with minimal side effects, but tolerance of it is low because of its burning and irritant effect, and it is expensive.
- Available in 0.05%, 0.1%, and 1% concentrations. In Saudi Arabia, only the 0.05% concentration is available in the pharmacies and higher concentrations should be prepared by a local pharmacy of the hospitals in tertiary centers.
- Relapse after stopping the medication is the problem, so long-term use is indicated, with a high dose of 1% during an acute attack. The dose should be reduced to 0.05% in between the attacks as a prophylactic. CsA has been shown to be less effective in cases with giant papillae.
- *Tacrolimus:* Tacrolimus ointment and drop uses in ophthalmic diseases are off label; it is FDA approved for dermatological use in a concentration of 0.1% and 0.03%. For dermatological use in children, only a 0.03% concentration is allowed for children aged 2 years and older, and it should be used for only a short period. It is a steroid-sparing agent and is found to be effective in cases refractory to topical CsA.

Other medications

- Topical acetylcysteine 5%–10% has been used to reduce mucus adherence to the cornea during acute exacerbations.
- *Rebamipide 2%* ophthalmic suspension is also found to be effective in reducing symptoms and signs in severe VKC and restores corneal damage in VKC. However, it is used as adjunct treatment, and its effect is visible after 5 weeks of its usage.

Surgical treatment

- Surgical treatment is recommended in cases of corneal involvement and large tarsal papillae resulting in ptosis.

Complications and treatment

- Variable incidence of keratoconus among children with VKC has been reported to be 2.1%–15%; therefore, in addition to treating VKC, one must closely monitor the corneal topography of both eyes of a VKC patient for early detection of keratoconus.
- Shield ulcer and plaque are common complications in severe cases, with a reported incidence of 3%–11%.
- In addition to aggressive medical therapy, corneal epithelial debridement, amniotic membrane transplantation (AMT), or both are recommended to treat shield ulcer and LSCD (Limbal Stem Cell Deficiency) and to prevent severe visual impairment due to the complications.
- Microbial keratitis secondary to shield ulcer has been reported, with an incidence of 9%–10%.
- Cornea scarring with reduced vision can be caused by healed shield ulcer, healed microbial keratitis, or LSCD. LSCD is secondary to the chronic inflammatory process and frequent eyelid rubbing against giant papillae that results in damaging limbal stem cells.

Cycloplegic Refraction

- One of the most common complications of VKC is astigmatism that can lead to decreased vision if not discovered and treated with glasses.
- Usually, VKC cases are managed by general ophthalmologists, and unfortunately, they forget to do cycloplegic refraction. It is recommended that every patient with VKC undergoes cycloplegic refraction at least once at first presentation.

- It is preferable for cycloplegic refraction to be done after the eye is quieted so the patient will be cooperative enough to open the eye and the reflex of the retinoscope will be clear.
- In the past two decades, a few new medications have been marketed to treat VKC; new biologics such as *topical calcineurin and IgE inhibitors* could be safe alternatives to corticosteroids in the treatment of VKC. Their efficacy has been compared and described in a few reviews and many industry-sponsored drug trials. They are promising but unfortunately have only short-term impact evaluations.

Section 2.0 Drug Therapy in Allergic Conjunctivitis

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been approved by the FDA and/or EMA but are not currently SFDA-registered,

2.1 Additions

After July 2020, there have been two new drugs for allergic conjunctivitis that have received FDA or EMA approval. Nevertheless, none of them was registered in the SFDA list and submitted to the CHI for evaluation. Hence, relevant information pertaining to this drug can be found in section 2.4.

2.2 Modifications

Since July 2020, the prescribing edits were modified to remove "Prior Authorization (PA)" from all medications. The prescribing edit "**PA**" was changed to "**MD**" for ciclosporin eye drops emulsion. The prescribing edit "**PA**" was changed to "**MD**" for corticosteroids' eye drops (Prednisolone acetate, Fluorometholone, Trehalose sodium hyaluronate). Tacrolimus ointment was added to the excel sheet.

2.3 Delisting

The medications below are no longer SFDA registered[13], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drugs in the disease - section 2*** *of CHI Allergic Conjunctivitis original clinical guidance*

- Dexpanthenol, sodium hyaluronate
- Ebastine
- Ectoin, sodium hyaluronate
- Glycerin, sodium carboxymethylcellulose

2.4 Other Drugs

2.4.1 Dexamethasone Ophthalmic Insert (Dextenza®)

- October 11, 2021. The FDA approved Ocular Therapeutix Inc.'s Supplemental New Drug Application (sNDA) that further extends Dextenza's (dexamethasone ophthalmic insert) 0.4 mg indications[14].
- The current approval of the drug to treat ocular itching associated with allergic conjunctivitis was based on the results of 3 randomized, multicenter, vehicle-controlled studies that included 255 patients with a positive history of ocular allergies and positive skin test reaction to perennial and seasonal allergens[14].
- The results of the 3 studies showed that Dextenza had lower mean ocular itching scores compared with the vehicle group at all time points throughout the study duration of up to 30 days[14].
- In 2 of the studies, higher percentages of patients had significant reductions in ocular itching on day 8 after the start of treatment, at 3-, 5-, and 7-minutes post-challenge in the Dextenza group compared to the vehicle group[14].

2.4.2 Cyclosporine Ophthalmic Emulsion (Verkazia® 0.1%)

- June 24, 2021. FDA approves eye drops for Vernal Keratoconjunctivitis in Adults and Children.
- The approval was supported by 2 trials demonstrating treatment efficacy in reducing ocular itching and inflammation in the cornea[15].
- The safety and efficacy of the emulsion were evaluated in 2 randomized, multi-center clinical trials. In the VEKTIS study, patients with severe VKC were randomized to receive cyclosporine ophthalmic emulsion 1 mg/mL either 4 times daily or 2 times daily and vehicle group. In the NOVATIVE study, patients with moderate to severe VKC received either QID cyclosporine ophthalmic emulsion 1 mg/mL or QID of cyclosporine ophthalmic emulsion 0.5 mg/mL and vehicle group for the first month[15].
- In both studies, patients randomized to the vehicle group were switched to receive Verkazia from month 4 to month 12 in the VEKTIS study and to receive cyclosporine ophthalmic emulsion 0.5 mg/mL QID or 1 mg/mL from month 1 to month 4 in the NOVATIVE study[15].

Section 3.0 Key Recommendations Synthesis

Pediatric allergic conjunctivitis

- Nonpharmacological measures include general environmental measures to reduce exposure to allergens (e.g., elimination of domestic dust, fungi, and pollen) and specific actions, such as the use of cold-water compresses, preservative-free artificial tears, and local cleansing with saline solution to wash the allergens from the conjunctiva and to contract the conjunctival vessels to relieve edema and hyperemia. In addition, sunglasses can be used to prevent contact with suspended allergens and for photophobia relief (grade of recommendation: A).[9]

- Topical treatment

- First-generation topical eye antihistamines act by blocking receptor H1; however, they are poorly tolerated and have limited effect and potency (grade of recommendation D).[9]

  Their combination with vasoconstrictors extends their therapeutic effect, although at the expense of rebound hyperemia and tachyphylaxis as undesirable common adverse effects. Long-term use of vasoconstrictors is not recommended, and these drugs should be administered with caution to patients with glaucoma, hyperthyroidism, or cardiovascular disease (grade of recommendation D).[9]

- Topical NSAIDs have proven efficacy against hyperemia and conjunctival itching (grade of recommendation A). Ketorolac is approved for the treatment of AC but has been reported to be less effective than **olopatadine** and **emedastine**. The use of topical NSAIDs in children is also limited by their burning sensation.[9]

- Topical ocular corticosteroids are not considered a first-choice therapy for AC, although drugs in lower concentrations (**fluorometholone**, **loteprednol**, and **rimexolone**) can be used to treat moderate inflammation. The drugs of choice for severe inflammation are **dexamethasone** and **prednisolone** (grade of recommendation B).[9]

- Topical nasal corticosteroids are not considered a treatment of choice for AC, but they can improve ocular symptoms by reducing the nasal-ocular reflex in patients with rhinoconjunctivitis. Mometasone **furoate, fluticasone furoate**, and **fluticasone plus azelastine furoate** can alleviate the symptoms of allergic rhinoconjunctivitis (grade of recommendation A).[9]

- Systemic treatment

- First-generation H1 antihistamines are not recommended, because of their sedative effect and anti-cholinergic activity. Second-generation drugs

(desloratadine, ebastine, loratadine, and rupatadine) have similar efficacy but a more manageable sedation profile and fewer adverse effects (grade of recommendation B).[9]

- Immunomodulators may be an option for severe cases that are refractory to topical treatment to avoid systemic corticosteroid use and its inherent adverse effects.[9]
- Both tacrolimus and cyclosporin act by inhibiting calcineurin (a calcium-dependent phosphatase), which activates the nuclear factor and causes proliferation and activation of T cells.[9]
- The use of T lymphocyte signal transduction inhibitors in the treatment of AKC in patients who are refractory to conventional therapy or other immunomodulatory therapy was shown to be effective in sparing the use of corticosteroids.[9]

Monoclonal antibodies

- The humanized anti-IgE monoclonal antibody **omalizumab**, which is indicated for the treatment of asthma and chronic urticaria, has also been shown to have an effect, although incomplete, on the control of severe VKC.[9]

Clinical monitoring: Ophthalmological assessments to assess AC control should be performed as follows: For *mild cases*, reassess every 4 weeks and maintain treatment until symptoms are resolved. For *intermittent and perennial moderate cases,* reassess every 4 weeks. For *severe cases,* reassess every 2 weeks.[9]

Selection of treatment methods

- *Allergic conjunctivitis:* The first option is antiallergic eye drops. A mast cell stabilizer can be combined with a histamine H1 receptor antagonist. During a period with severe symptoms, steroid eye drops are additionally administered. In SAC, administration of antiallergic eye drops is started around 2 weeks prior to the predicted day of the start of flying pollen or at the time when few symptoms appear so that the symptoms decrease during the peak time of flying pollen.[2]
- *Vernal keratoconjunctivitis:* For moderate or more severe cases such those for which antiallergic eye drops alone are not sufficiently effective, immunosuppressive eye drops are additionally administered.[2]

  When improvement cannot be achieved, addition of steroid eye drops or switching to tacrolimus eye drops is recommended. Depending on the severity of the symptoms, a steroid oral medicine and subtarsal conjunctival steroid injection or surgical treatment should be considered. When the symptoms are alleviated, the dose of steroid eye drops, or the number of instillations should be gradually decreased. After remission is attained, antiallergic eye drops with or without immunosuppressive eye drops can be used for long-term control.[2]

Vernal Keratoconjunctivitis (VKC)

- As first-line pharmacological therapy, dual-acting agents (e.g., olopatadine, azelastine hydrochloride, epinastine, ketotifen) may be considered rather than monotherapy with antihistamines or mast cell stabilizers (e.g., sodium cromoglycate, nedocromil, lodoxamide), depending on formulary, local recommendations, and availability.[11]
- Short-pulse *topical* corticosteroids are effective to tackle inflammation and manage acute exacerbations or when the cornea is involved and should be considered for patients with moderate-to-severe disease either alone, as an add-on to topical CsA, or as rescue therapy under the supervision of an ophthalmologist, and repeat cycles avoided, where possible, to prevent dependency.[11]
- The use of high-frequency or oral corticosteroids (in short pulses) may be appropriate for patients with persistent corneal complications or non-response to prior treatments but should only be prescribed by a clinician experienced in the use of these medications.[11]
- Topical immunomodulators, such as CsA (Ciclosporin A), should be taken into consideration for patients dealing with moderate to severe or persistent VKC.[11]
- Advanced systemic treatments (e.g., immunomodulators, biologics) should only be prescribed in appropriate settings (e.g., patients with recalcitrant disease or involving other allergic manifestations) and by clinicians experienced in their use. Allergen-specific immunotherapy is only recommended where there is clearly defined systemic hypersensitivity to an identified allergen.[11]

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Allergic Conjunctivitis report** and aims to provide recommendations to aid in the management of Allergic Conjunctivitis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Allergic Conjunctivitis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Allergic Conjunctivitis Scope

Section	Rationale/updates
N/A	Japanese guidelines for allergic conjunctival diseases 2020[2] Addition of: - Prophylaxis: self-care (Avoidance and elimination methods by types of antigens, Self-care for allergic conjunctivitis - Self-care for allergic conjunctivitis (Effect of glasses for prevention of pollens, contact lens wear, Eye washing by artificial tear) Treatment: medical care - Fundamentals of treatment - Antiallergic eye drops - Eye drops - Oral medicines - Eye ointments - Sub-tarsal conjunctival injection of steroid suspension - Immunosuppressive eye drops - Surgical treatment **Selection of treatment methods** - Allergic conjunctivitis: the first option is antiallergic eye drops. A mast cell stabilizer can be combined with a histamine H1 receptor antagonist. During a period with severe symptoms, steroid eye drops are additionally administered. In SAC, administration of antiallergic eye drops is started around 2 weeks prior to the predicted day of the start of flying pollen or at the time when few symptoms appear so that the symptoms decrease during the peak time of flying pollen. Introductory points for medical specialists - For a case of conjunctivitis presenting with ocular itching as the major symptom, anti-allergic ophthalmic eye drops can be prescribed. However, in cases where symptoms are not alleviated after 1-2 weeks of treatment, it is advisable for the physician to recommend the patient to visit an ophthalmology department considering differential diagnosis of a bacterial or viral infection. - When the therapeutic effects are insufficient, steroid eye drops are administered in combination. However, continued use of steroid eye drops may cause increased intraocular pressure or exacerbation of ocular infections; hence, regular examinations by an ophthalmologist are required. - Contact lens wear may aggravate symptoms such as ocular itching,

	hyperemia, and ocular discharge, and may often need to be discontinued prior to treatment under consultation with a family ophthalmologist. - Prescription of immunosuppressive eye drops requires management by ophthalmologist; therefore, refractory pediatric patients with suspected VKC or AKC should be recommended to be examined in an ophthalmology department. ➔ *Treatment of ACDs: proliferative (vernal keratoconjunctivitis). (fig 19)* ➔ *Tables 3-6* EYE DROPS: Epinastine hydrochloride, Fluorometholone EYE OINTMENT: Prednisolone
N/A	Brazilian guidelines for the monitoring and treatment of pediatric allergic conjunctivitis 2022[9] ***RESULTS AND RECOMMENDATIONS*** AC diagnosis ➢ The diagnosis of ocular allergy is based on family and personal history of atopy, symptoms, clinical signs, and, eventually, additional tests. ➢ Ocular allergy is usually bilateral, with itching, accompanied by tearing and a burning sensation, as the most common symptom. Visual disturbance and photophobia can occur in severe cases. ➢ A slit-lamp ophthalmological examination may reveal watery or mucoid secretions, eyelid edema, chemosis, papillary hypertrophy in the palpebral conjunctiva, conjunctival hyperemia, limbal nodules, keratitis, and corneal involvement. ➢ Complementary tests, such as skin tests, and measurement of IgE specific levels in serum or tears can be requested. ➢ However, skin tests tend to be negative in the absence of an association with rhinitis, and the IgE dosages may not be conclusive, since 24% of patients may be sensitive to multiple allergens (2). Thus, cytological diagnosis is usually reserved for research purposes. AC treatment ➢ The initial treatment consists of nonpharmacological measures that aim to prevent or minimize contact between the allergen and the conjunctiva. ➢ If nonpharmacological measures are insufficient, topical pharmacological treatment is started with antihistamines, mast cell membrane stabilizing agents, multiple-action drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. Topical treatment summarized in table 1. ➢ Systemic allergen-specific immunotherapy can be used to suppress or regulate the immune response. Immunotherapy not only helps to control

	symptoms but also slows the progression of allergic disease. Disease control criteria ➢ The present guidelines use the control criteria proposed by the Document on AC (DECA). The control criteria are based on the presence of ocular symptoms within 2 weeks of the evaluation, the visual analog scale (VAS) score, and the ophthalmological examination, with conjunctival hyperemia graded by the Efron scale. Applicability of treatment modalities for allergic conjunctivitis according to its severity added. ➔ Treatment algorithm
N/A	Management of Vernal Keratoconjunctivitis in *Children* in the United Kingdom: A *Review* of the Literature and Current Best Practice Across Six Large United Kingdom Centers[10] ➢ Symptoms and Diagnosis ➢ Severity and classification of VKC (Summary in table 2) ➢ Initial Treatment ➢ Long-term Management and Follow-up ➢ Supportive Care Treatment stepladder for VKC
N/A	Novel Insights in the Management of Vernal Keratoconjunctivitis (VKC): European Expert Consensus Using a Modified Nominal Group Technique 2023[16] • Staged Assessment of VKC: The group distinguished common signs and symptoms of VKC of which different specialties should be aware as shown in figure 1. ➢ Stepwise Management Approach Based on Severity and Progression of VKC: The EUR-VKC Group agreed that the patient and family/caregiver should always be provided with supportive care and education, with an emphasis on avoiding triggers or exacerbators and allergens, lid hygiene, and use of cold compresses and ocular lubricants/artificial tears (without preservatives, since these can cause allergies or may damage the corneal surface. ➢ First-line pharmacological therapy, dual-acting agents (e.g., **olopatadine**, **azelastine hydrochloride, epinastine, ketotifen**) ➢ Short-pulse topical corticosteroids are effective to tackle inflammation and manage acute exacerbations or when the cornea is involved, and should be considered for patients with moderate-to-severe disease either alone, as an add-on to topical CsA, or as rescue therapy • Measuring IOP before starting treatment allows the physician to monitor

	changes over time and identify any potential steroid-induced complications. Some 'soft' corticosteroids (e.g., **loteprednol**, **hydrocortisone**) may not completely resolve VKC exacerbations, and long-term treatment can lead to corticosteroid dependency. • 'High-potency' topical corticosteroids (e.g., **dexamethasone**), used as a pulse therapy for 3–5 days without tapering, could be more efficacious in resolving exacerbations and less likely to increase IOP than the longer-term use of 'soft' corticosteroids. ➢ Topical immunomodulators (e.g., CsA) should be considered for patients with moderate-to-severe or persistent VKC, as well as those with corticosteroid dependency, to provide long-term control. If short-pulse corticosteroids are used frequently, for a period of [3 months, then topical CsA should be considered for long-term control. Topical CsA has shown a marked corticosteroid-sparing effect, potentially allowing control of symptomatology without corticosteroids. CsA may not be appropriate for patients with moderate VKC without other signs of progression or risk of recurrences. ➢ Oral antihistamines may be used as adjunctive therapy for mild flare-ups or in the case of allergic rhinitis, if required. Advanced systemic treatments (e.g., immunomodulators, biologics) should only be prescribed in appropriate settings (e.g., patients with recalcitrant disease or involving other allergic manifestations) and by clinicians experienced in their use. Allergen-specific immunotherapy is only recommended where there is clearly defined systemic hypersensitivity to an identified allergen. (Full list of recommendations summarized in a figure). ➢ Adding other treatments for VKC and long-Term Management and Flare-Ups of VKC. ➢ Key Information to Communicate with Patients and Caregivers on VKC: • Sunlight, wind, salty water, dust, and heat can exacerbate VKC, so the use of sunglasses, hats, visors, and swimming goggles may be considered. Furthermore, an air-filtration system in the home may provide relief. • Common allergens can exacerbate VKC, and frequently washing the hands, face and hair can reduce exposure to these allergens. • Cold compresses and preservative-free artificial tears can provide symptomatic relief.
N/A	AlHarkan DH. Management of vernal keratoconjunctivitis in *children* in Saudi Arabia. *Oman J Ophthalmol*. 2020;13(1):3-12. Published 2020 Feb 17. doi: 10.4103/ojo.OJO_263_2018[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7050462/?report=reader

	➢ Pediatric doctors and primary health-care providers prescribe antiallergic medication (including topical administration of antihistamine, mast cell inhibitors, or combinations of both) safely to patients presenting with itching and redness. ➢ Treatment of VKC needs a good understanding of the disease and its chronic course. The parents should be educated about the importance of good compliance with medications and the chronic nature of the disease. **Nonpharmacological Management** ➢ Topical lubrication with artificial tears is important as a long-term management of VKC patients, during both active and inactive phases. First, it can reduce the symptoms of itching by a cooling effect. ➢ During an acute attack and active VKC, it can wash out the inflammatory mediators present in the tear and by this, reduce inflammation. **Pharmacological Management** ➢ The focus of the medical management of VKC is to relieve the debilitating symptoms, reduce the signs, and prevent complications. ➢ Antihistamine: Second-generation H (1)-antihistamines are among the most prescribed medicines to treat allergic conjunctivitis, including VKC in children. *Emedastine* and *Levocabastine* (LEVO), have been reviewed and found to be safe and well tolerated. ➢ Mast cell stabilizers: Sodium cromoglycate: and Lodoxamide. ➢ The combination of antihistamine and mast cell stabilizers such as azelastine and olopatadine is safe for children aged 3 years and older. ➢ *Steroids:* These are the most potent and effective medications that can be applied as eye drops as well as ointment to treat moderate-to-severe cases of VKC (severe itching with inflamed conjunctiva, presence of limbal infiltrates, corneal involvement, and presence of giant papillae). ➢ *Immunosuppressive eye drops: Cyclosporine A (CsA),* It is a nonsteroidal immune modulator and is most effective in treating VKC with minimal side effects, but tolerance of it is low because of its burning and irritant effect, and it is expensive. *Tacrolimus:* Tacrolimus ointment and drop uses in ophthalmic diseases are off label; it is FDA approved for dermatological use in a concentration of 0.1% and 0.03%. For dermatological use in children, only a 0.03% concentration is allowed for children aged 2 years and older, and it should be used for only a short period. It is a steroid-sparing agent and is found to be effective in cases refractory to topical CsA. Other medications: Rebamipide 2% ophthalmic suspension is also found to be effective in reducing symptoms and signs in severe VKC and restores corneal damage in VKC.

	Surgical treatment: recommended in cases of corneal involvement and large tarsal papillae resulting in ptosis. **Complications and treatment:** In addition to aggressive medical therapy, corneal epithelial debridement, amniotic membrane transplantation (AMT), or both are recommended to treat shield ulcer and LSCD (Limbal Stem Cell Deficiency) and to prevent severe visual impairment due to the complications. **Cycloplegic Refraction**: ➢ One of the most common complications of VKC is astigmatism that can lead to decreased vision if not discovered and treated with glasses. ➢ Usually, VKC cases are managed by general ophthalmologists, and unfortunately, they forget to do cycloplegic refraction. It is recommended that every patient with VKC undergoes cycloplegic refraction at least once at first presentation. ➢ A few new medications have been marketed to treat VKC; new biologics such as *topical calcineurin and IgE inhibitors* could be safe alternatives to corticosteroids in the treatment of VKC.

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Allergic Conjunctivitis:

Query	Filters	Search Details	Results
((((((((((((((((((((allergic conjunctivitis[MeSH Terms]) OR (allergic conjunctivitis[Title/Abstract])) OR (Conjunctivitis, Atopic[Title/Abstract])) OR (Atopic Conjunctivitides[Title/Abstract])) OR (Atopic Conjunctivitis[Title/Abstract])) OR (Conjunctivitides, Atopic[Title/Abstract])) OR (Allergic Conjunctivitis[Title/Abstract])) OR (Allergic Conjunctivitides[Title/Abstract])) OR (Conjunctivitides, Allergic[Title/Abstract])) OR (Conjunctivitis, Vernal[Title/Abstract])) OR (Conjunctivitides, Vernal[Title/Abstract])) OR (Vernal Conjunctivitides[Title/Abstract])) OR (Vernal	Guideline, in the last 5 years	("conjunctivitis, allergic"[MeSH Terms] OR "allergic conjunctivitis"[Title/Abstract] OR "conjunctivitis atopic"[Title/Abstract] OR (("Atopic"[All Fields] OR "atopical"[All Fields] OR "atopics"[All Fields]) AND "Conjunctivitides"[Title/Abstract]) OR "atopic conjunctivitis"[Title/Abstract] OR (("conjunctivities"[All Fields] OR "Conjunctivitis"[MeSH Terms] OR "Conjunctivitis"[All Fields] OR "Conjunctivitides"[All Fields]) AND "Atopic"[Title/Abstract]) OR "allergic conjunctivitis"[Title/Abstract] OR "allergic conjunctivitides"[Title/Abstract] OR (("conjunctivities"[	2

Conjunctivitis[Title/Abstract])) OR (Keratoconjunctivitis, Vernal[Title/Abstract])) OR (Keratoconjunctivitides, Vernal[Title/Abstract])) OR (Vernal Keratoconjunctivitides[Title/Abstract])) OR (Vernal Keratoconjunctivitis[Title/Abstract])) OR (Conjunctivitis, Giant Papillary[Title/Abstract])) OR (Conjunctivitides, Giant Papillary[Title/Abstract])) OR (Giant Papillary Conjunctivitides[Title/Abstract])) OR (Giant Papillary Conjunctivitis[Title/Abstract])) OR (Papillary Conjunctivitides, Giant[Title/Abstract])) OR (Papillary Conjunctivitis, Giant[Title/Abstract])		All Fields] OR "Conjunctivitis"[MeSH Terms] OR "Conjunctivitis"[All Fields] OR "Conjunctivitides"[All Fields]) AND "Allergic"[Title/Abstract]) OR "conjunctivitis vernal"[Title/Abstract] OR (("conjunctivities"[All Fields] OR "Conjunctivitis"[MeSH Terms] OR "Conjunctivitis"[All Fields] OR "Conjunctivitides"[All Fields]) AND "Vernal"[Title/Abstract]) OR ("Vernal"[All Fields] AND "Conjunctivitides"[Title/Abstract]) OR "vernal conjunctivitis"[Title/Abstract] OR "keratoconjunctivitis vernal"[Title/Abstract] OR (("Keratoconjunctivitis"[MeSH Terms] OR "Keratoconjunctivitis"[All Fields] OR "Keratoconjunctivitides"[All Fields]) AND	

		"Vernal"[Title/Abstract]) OR ("Vernal"[All Fields] AND "Keratoconjunctivitides"[Title/Abstract]) OR "vernal keratoconjunctivitis"[Title/Abstract] OR "conjunctivitis giant papillary"[Title/Abstract] OR ((("conjunctivities"[All Fields] OR "Conjunctivitis"[MeSH Terms] OR "Conjunctivitis"[All Fields] OR "Conjunctivitides"[All Fields]) AND "giant papillary"[Title/Abstract]) OR (("giants"[All Fields] OR "gigantism"[MeSH Terms] OR "gigantism"[All Fields] OR "Giant"[All Fields] OR "giants"[All Fields]) AND "papillary conjunctivitides"[Title/Abstract]) OR "giant papillary conjunctivitis"[Title/Abstract] OR ((("papillaries"[All Fields] OR "Papillary"[All	

		Fields]) AND ("conjunctivities"[All Fields] OR "Conjunctivitis"[MeSH Terms] OR "Conjunctivitis"[All Fields] OR "Conjunctivitides"[All Fields])) AND "Giant"[Title/Abstract]) OR (("papillaries"[All Fields] OR "Papillary"[All Fields]) AND "conjunctivitis giant"[Title/Abstract])) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm

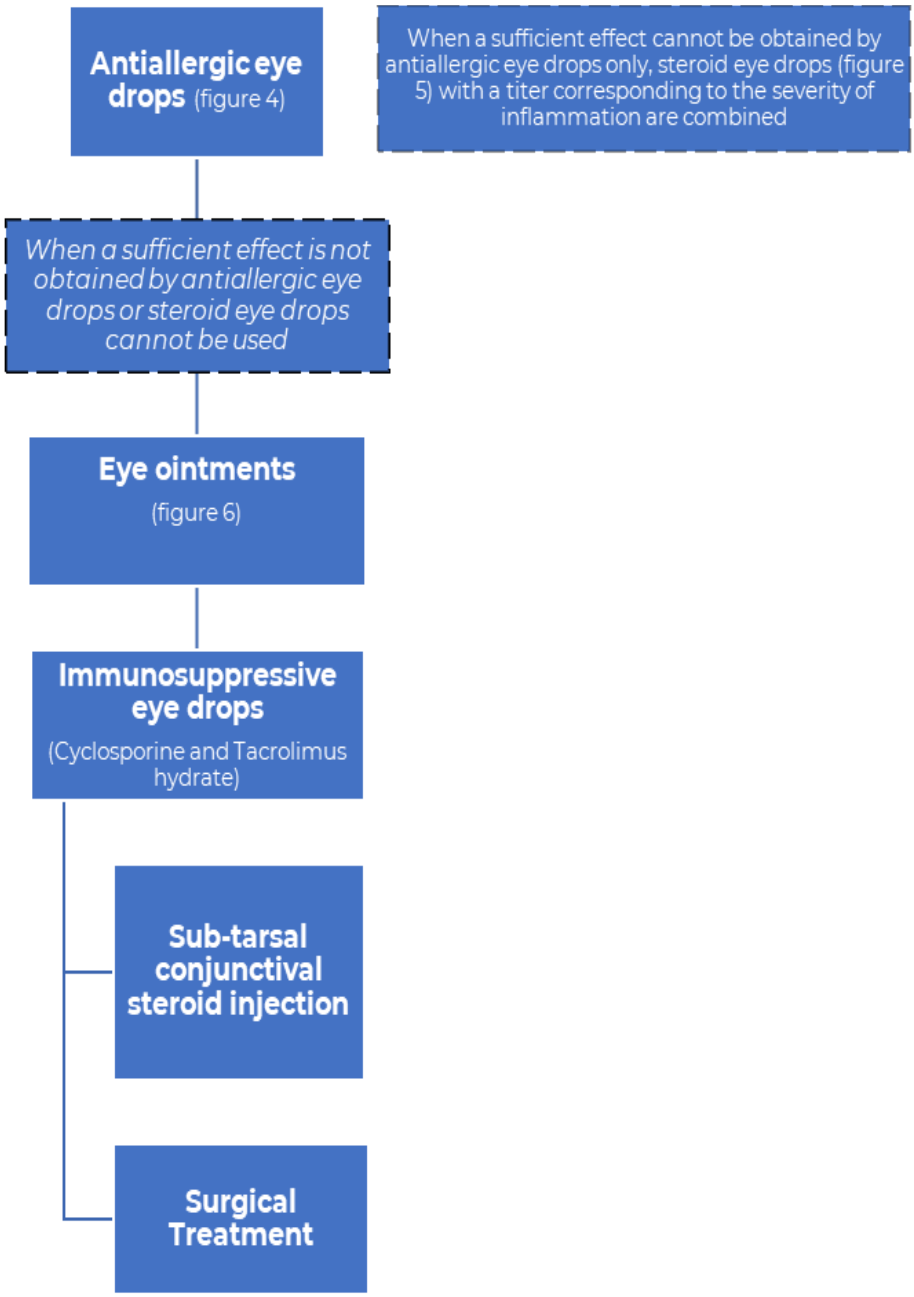

Figure 4. *Treatment of Allergic Conjunctival Diseases (ACDs)*

Mild	Moderate	Severe
• Exposure avoidance/cold compresses • Topical dual-action agents (mast-cell stabilizers. topical antihistamines) • (Ocular lubricants, unless other simultaneous high-frequency treatment) • Oral antihistamines, if indicated if child is already receiving, can be continued	• Short pulses of topical steroids • Topical calcineurin inhibitors (e.g. ciclosporin A)	• High-frequency/high potency topical steroids • Mucolytic (acetylcysteine) • Surgery, including supratarsal steroid injection • Oral steroids: 3 days max (e.g. prednisolone) • Systemic biologicals/calcineurin inhibtors

Figure 5. *Treatment Stepladder for Vernal Keratoconjunctivitis (VKC)*