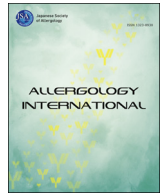




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Invited review article

Japanese guidelines for allergic conjunctival diseases 2017[☆]

Etsuko Takamura ^{a,*}, Eiichi Uchio ^b, Nobuyuki Ebihara ^c, Shigeaki Ohno ^d, Yuichi Ohashi ^e,
Shigeki Okamoto ^f, Naoki Kumagai ^g, Yoshiyuki Satake ^h, Jun Shoji ⁱ, Yayoi Nakagawa ^j,
Kenichi Namba ^d, Kazumi Fukagawa ^{k,l}, Atsuki Fukushima ^m, Hiroshi Fujishima ⁿ, The
Japanese Society of Allergology

^a Department of Ophthalmology, Tokyo Women's Medical University, School of Medicine, Tokyo, Japan^b Department of Ophthalmology, Fukuoka University, School of Medicine, Fukuoka, Japan^c Department of Ophthalmology, Juntendo University Urayasu Hospital, Chiba, Japan^d Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Hokkaido, Japan^e Department of Ophthalmology, Ehime University School of Medicine, Ehime, Japan^f Okamoto Eye Clinic, Ehime, Japan^g Kumagai Eye Clinic, Yamaguchi, Japan^h Department of Ophthalmology, Tokyo Dental College, Ichikawa General Hospital, Chiba, Japanⁱ Division of Ophthalmology, Department of Visual Sciences, Nihon University, School of Medicine, Tokyo, Japan^j Nakagawa Eye Clinic, Osaka, Japan^k Ryogoku Eye Clinic, Tokyo, Japan^l Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan^m Department of Ophthalmology, Kochi Medical School, Kochi, Japanⁿ Department of Ophthalmology, Tsurumi University School of Dental Medicine, Kanagawa, Japan

ARTICLE INFO

Article history:

Received 29 August 2016

Available online xxx

Keywords:

Allergic conjunctivitis

Antiallergic eye drop

Atopic keratoconjunctivitis

Giant papillary conjunctivitis

Vernal keratoconjunctivitis

ABSTRACT

The definition, classification, pathogenesis, test methods, clinical findings, criteria for diagnosis, and therapies of allergic conjunctival disease are summarized based on the Guidelines for Clinical Management of Allergic Conjunctival Disease (Second Edition) revised in 2010. Allergic conjunctival disease is defined as “a conjunctival inflammatory disease associated with a Type I allergy accompanied by some subjective or objective symptoms.” Allergic conjunctival disease is classified into allergic conjunctivitis, atopic keratoconjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis. Representative subjective symptoms include ocular itching, hyperemia, and lacrimation, whereas objective symptoms include conjunctival hyperemia, swelling, folliculosis, and papillae. Patients with vernal keratoconjunctivitis, which is characterized by conjunctival proliferative changes called giant papilla accompanied by varying extents of corneal lesion, such as corneal erosion and shield ulcer, complain of foreign body sensation, ocular pain, and photophobia. In the diagnosis of allergic conjunctival diseases, it is required that type I allergic diathesis is present, along with subjective and objective symptoms accompanying allergic inflammation. The diagnosis is ensured by proving a type I allergic reaction in the conjunctiva. Given that the first-line drug for the treatment of allergic conjunctival disease is an antiallergic eye drop, a steroid eye drop will be selected in accordance with the severity. In the treatment of vernal keratoconjunctivitis, an immunosuppressive eye drop will be concomitantly used with the abovementioned drugs.

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[☆] This article is an updated version of “Japanese guideline for allergic conjunctival diseases” published in *Allergol Int* 2011;60:191–203.

* Corresponding author. Department of Ophthalmology, Tokyo Women's Medical University, School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.

E-mail address: takamura.etsuko@twmu.ac.jp (E. Takamura).

Peer review under responsibility of Japanese Society of Allergology.

<http://dx.doi.org/10.1016/j.alit.2016.12.004>

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1. Definition and classification of allergic conjunctival disease

1.1. Definition

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 allergic conjunctival disease even if other types of inflammatory reactions are involved.¹

1.2. Classification

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 (Fig. 1).

1.2.1. Allergic conjunctivitis (AC) (Fig. 2)

Allergic conjunctival diseases without proliferative changes in the conjunctiva include seasonal allergic conjunctivitis (SAC) where symptoms appear in a seasonal manner and perennial allergic conjunctivitis (PAC) where symptoms persist throughout the year.

1.2.2. Atopic keratoconjunctivitis (AKC) (Fig. 3)

AKC is a chronic allergic conjunctival disease that may occur in patients with facial atopic dermatitis. Giant papillae may be present although many AKC cases have no proliferative changes.

1.2.3. Vernal keratoconjunctivitis (VKC) (Fig. 4)

VKC is characterized by conjunctival proliferative changes such as papillary hyperplasia of the palpebral conjunctiva or its enlargement, and swelling or limbal gelatinous hyperplasia. Many VKC cases accompany atopic dermatitis. Corneal lesions with various severities including superficial punctate keratitis, corneal erosion, persistent corneal epithelial defect, corneal ulcers, or corneal plaque have been observed in VKC.

1.2.4. Giant papillary conjunctivitis (GPC) (Fig. 5)

GPC is conjunctivitis that accompanies proliferative changes in the upper palpebral conjunctiva induced by mechanical irritations such as contact lenses, ocular prosthesis, or surgical sutures. Clinically, GPC differs from VKC by the absence of a corneal lesion and by having a different papillary form.

2. Epidemiology of ACD

In surveys of the entire population conducted by the Allergy Integrated Project Epidemiologic Investigation Group of the Ministry of Health and Welfare in 1993, the proportion of persons with bilateral ocular itching was 16.1% in children aged less than 15 and 21.1% in adults. The proportion of persons with allergic conjunctival diseases diagnosed by ophthalmologists was 12.2% in children and 14.8% in adults. From these results, the proportion of persons with allergic conjunctival diseases in the entire population is estimated to be about 15–20%.

A research group on allergic ocular disease of the Japan Ophthalmologists Association conducted epidemiologic surveys of all patients with allergic conjunctival diseases that were treated at 28 facilities (7 university attached hospitals, 5 general hospitals, and

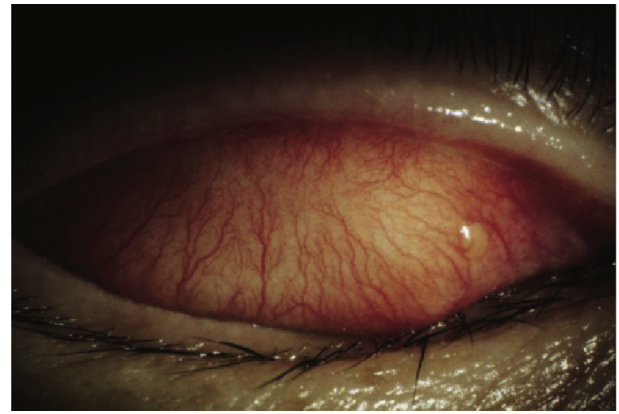


Fig. 2. Upper palpebral conjunctival findings in AC. Mild hyperemia and edema are present.

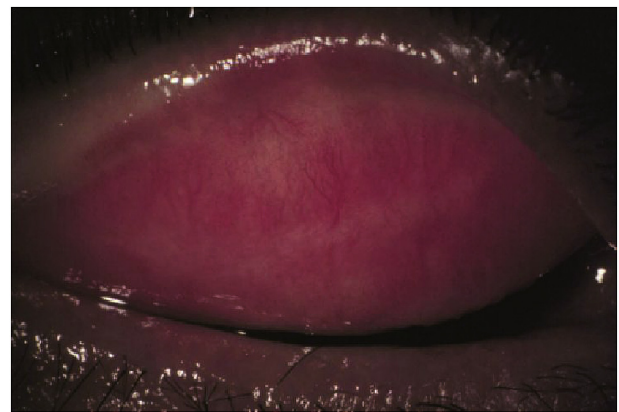


Fig. 3. Upper palpebral conjunctival findings in AKC. Hyperemia, opacity, and subconjunctival fibrosis are present.

16 ophthalmic hospitals and clinics) all over Japan during the period from January 1, 1993 to December 31, 1995. They found that female patients with SAC or PAC outnumbered male patients by 2: 1, whereas male patients with VKC outnumbered female patients by 2: 1. The number of patients with ACD was maximum at the age of 10 and the incidence decreased with aging (Fig. 6). The main subjective symptoms were an ocular itching, ocular hyperemia, eye discharge, and a foreign body sensation in each disease type. In SAC,

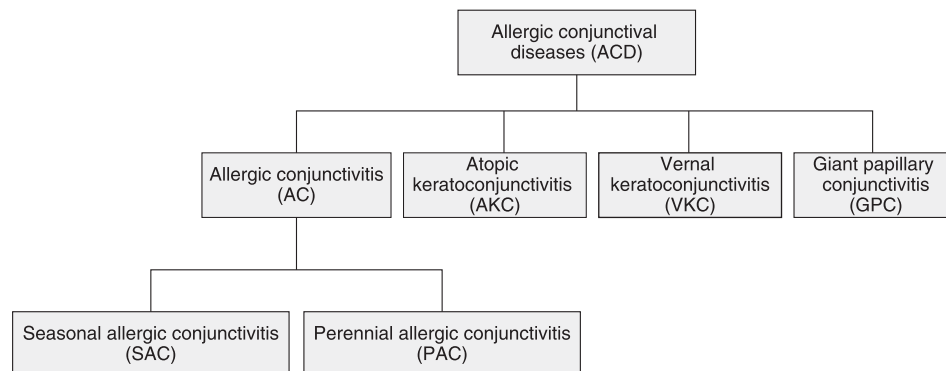


Fig. 1. Classification of ACD. ACD is classified as follows: (i) AC without proliferative change, (ii) AKC complicated with atopic dermatitis, (iii) VKC with proliferative changes, and (iv) GPC induced by irritation of a foreign body. Allergic conjunctivitis is subdivided into SAC and PAC according to the period of onset of the symptoms.

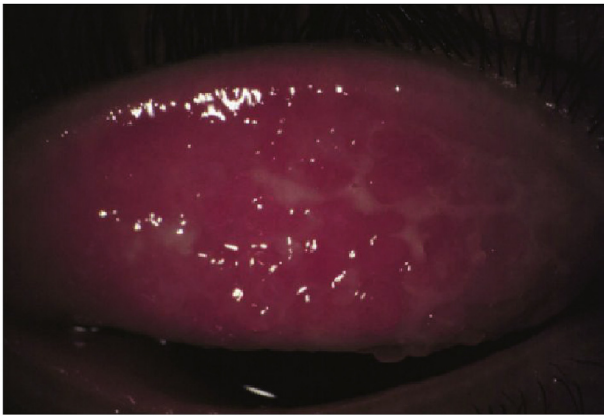


Fig. 4. Upper palpebral conjunctival findings in VKC. Conjunctival hyperemia, conjunctival edema, eye discharge, formation of giant papillae are present.

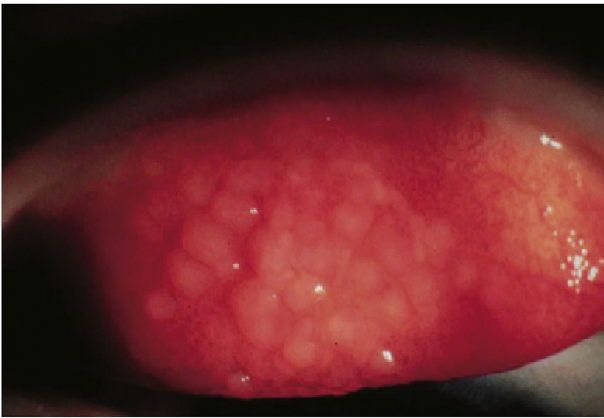


Fig. 5. Upper palpebral conjunctival findings in GPC. Hyperemia and dome-like giant papillae are present.

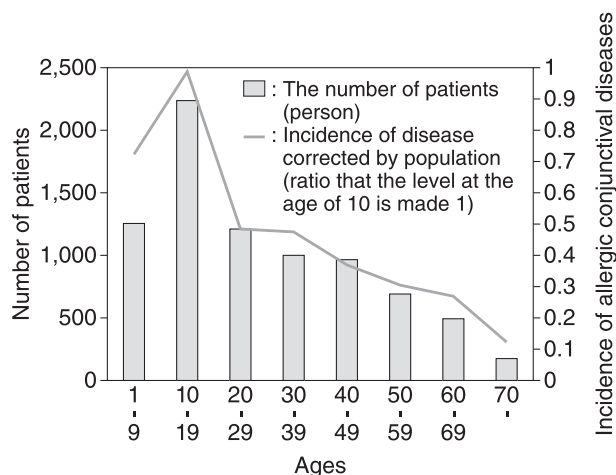


Fig. 6. Age distribution of patients with allergic conjunctival diseases. The number of patients with allergic conjunctival diseases who contacted the facilities was maximum at the age of 10 and the number decreased with aging. The peak incidence of each disease was also at the age of 10 and the incidence decreased with aging. (Incidence is calculated by dividing the number of treated patients in each age group by the entire population of the same age group in Japan. The incidence at the age of 10 is made 1 and the result is expressed as ratio.)

Adapted from reference 1.

symptoms of allergic rhinitis such as sneezing, rhinorrhea, nasal blockade were found in many cases.

3. Pathophysiology

The pathological conditions of ACD with lesions in the conjunctiva are assumed to be caused by interactions between various immune system cells and resident cells, which are mediated by physiologically active substances (e.g. histamine and leukotriene), cytokines, and chemokines. Eosinophils are the main effector cells in ACD. Various cytotoxic proteins released from eosinophils infiltrating locally into the conjunctiva are thought to cause keratoconjunctival disorders such as severe AKC and VKC.

It is also speculated that keratoconjunctival resident cells may be involved in the etiology of ACD by cytokine-stimulated production of chemokines such as eotaxin^{2,3} and TARC,⁴ which cause eosinophil and Th2 cell migrations from the circulation respectively.

4. Test methods

The objective of tests is to prove a type I allergic reaction in the conjunctiva and in the whole body. Clinical test methods for proving type I allergic reactions in the conjunctiva include the identification of eosinophils in the conjunctiva, instillation provocation test, and total IgE antibody measurements in lacrimal fluid. Systemic allergy tests detect antigen specific IgE antibodies in the skin and serum.

4.1. Identification of eosinophils in the conjunctiva

Eye discharge or ocular secretions collected using spatulas and tweezers, are smeared onto glass slides, then stained by Hansel or Giemsa staining methods, and observed under an optical microscope.⁵

4.2. Instillation provocation test

When an antigen can be presumed by skin test or serum antigen specific IgE antibody measurements, this test confirms the presence of conjunctivitis by instillation of a solution of the known antigen. If itching or hyperemia follows, the case is evaluated as being positive.

4.3. Total IgE antibody measurement in lacrimal fluid

A kit is commercially available to measure the level of total IgE antibody in lacrimal fluid using an immunochromatography.⁶

5. The clinical feature and evaluation criteria

5.1. Subjective symptoms

Representative subjective symptoms for ACD are itching, foreign body sensation, and eye discharge.

Itching is the most characteristic symptoms in ACD, but some patients complain of a foreign body sensation instead. The foreign body sensation is frequently present in ACD. Aside from cases where slight itching is felt as a foreign body sensation, it is very likely that when many conjunctival papillae sweep the cornea at the time of blinking, a foreign body sensation may occur. In ACD lymphocytes and eosinophils account for the majority of inflammatory cells, while neutrophils are few, serous and mucous discharge is often present, and the nature of the discharge differs from the purulent discharge associated with bacterial conjunctivitis and viscous and serous discharges found in viral conjunctivitis.

5.2. Objective symptoms

Conjunctival hyperemia with dilated conjunctival vessels is the most frequent conjunctival finding. Conjunctival swelling is a finding that is induced by circulatory failure of the palpebral conjunctival vessels and lymphatic vessels. And in many cases,

conjunctival opacity is accompanied. A conjunctival follicle is a lymphoid follicle seen under the lower palpebral conjunctival epithelium. This finding can be discriminated from papillae by the condition of a smooth dome-like prominence, which is surrounded by vessels. Conjunctival papillae are originated from epithelial proliferation in response to inflammation, in which the epithelium itself is hypertrophic. A vascular network is present from the center of the prominence, although this network is seen at the upper palpebral conjunctival fornix physiologically. Papillae of 1 mm or more in diameter, called giant papillae, are fibrous proliferative tissues found typically in VKC and GPC, and a large number of inflammatory cells such as lymphocytes, mast cells, and eosinophils are observed under the epithelium. Conjunctival edema is caused by leakage of plasma components from the vessels. Horner-Trantas dots found at the limbal region are small prominences induced by degeneration of proliferated conjunctival epithelium, in which congregated eosinophils may be present. Corneal complications in severe cases include superficial punctate keratitis, which is a partial defect of the corneal epithelium, exfoliated superficial punctate

keratitis, and shield ulcer (shield-shape ulcer), which is a prolonged corneal epithelial defect.

5.3. Clinical evaluation criteria of objective symptoms

Major objective symptoms in each site of the palpebral conjunctiva, bulbar conjunctiva, limbal conjunctiva, and cornea were graded for severity and the clinical evaluation criteria were made⁷ (Table 1).

5.3.1. Palpebral conjunctiva

The items evaluated in palpebral conjunctival findings are hyperemia, swelling, follicles, papillae, and giant papillae. The criteria in each item are the density of dilated blood vessels for hyperemia (Fig. 7), the scale and the presence or absence of opacity for swelling (Fig. 8), the number of follicles in either side inferior palpebral conjunctiva where more follicles are observed than in the other side for follicle (Fig. 9). Papillae are evaluated according to their diameter (Fig. 10). In case with papillae of 1 mm or more in diameter, it is regarded as giant papillae (Fig. 11), which are eval-

Table 1
Clinical evaluation criteria of allergic conjunctival diseases.

Palpebral conjunctiva	Hyperemia	Severe Moderate Mild None	Impossible to distinguish individual blood vessels Dilatation of many vessels Dilatation of several vessels No manifestations
	Swelling	Severe Moderate Mild None	Diffuse marked edema Diffuse mild edema Localized edema No manifestations
	Follicle	Severe Moderate Mild None	20 or more follicles 10–19 follicles 1–9 follicles No manifestations
	Papillae [†]	Severe Moderate Mild None	Diameter ≥ 0.6 mm Diameter 0.3–0.5 mm Diameter 0.1–0.2 mm No manifestations
	Giant papillae	Severe Moderate Mild None	Elevated papillae in 1/2 or more of upper palpebral conjunctiva Elevated papillae in less than 1/2 of upper palpebral conjunctiva Flat giant papillae No manifestations
Bulbar conjunctiva	Hyperemia	Severe Moderate Mild None	Vasodilatation of all vessels Dilation of many vessels Dilation of several vessels No manifestations
	Chemosis	Severe Moderate Mild None	Cyst-like chemosis of entire conjunctiva Diffuse thin chemosis Partial conjunctival swelling No manifestations
Limbus	Swelling	Severe Moderate Mild None	In $\geq 2/3$ of circumference In 1/3 to 2/3 of circumference In less than 1/3 of circumference No manifestations
	Horner-Trantas dots	Severe Moderate Mild None	≥ 9 dots 5–8 dots 1–4 dots No manifestations
Cornea	Epithelial disorder	Severe Moderate Mild None	Shield ulcer or epithelial erosion Superficial punctate keratitis with filamentary debris Superficial punctate keratitis No manifestations

[†] In cases having giant papillae, papillae and giant papillae should be graded simultaneously.

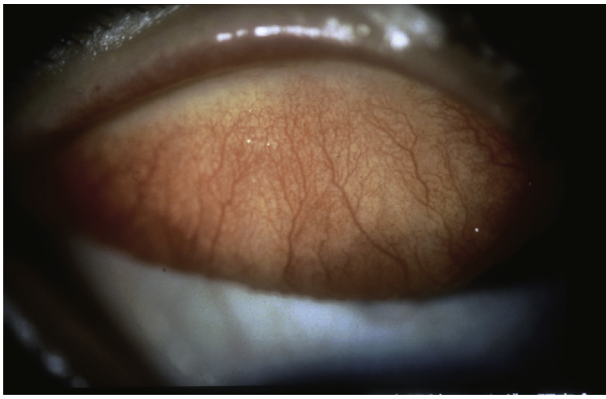


Fig. 7. Palpebral conjunctival hyperemia (moderate).
Source: reference.⁷

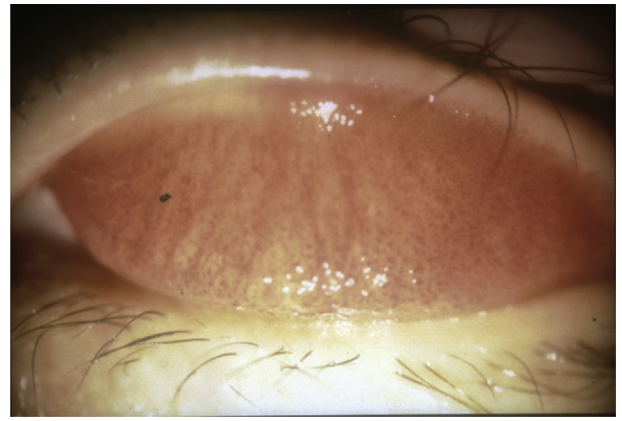


Fig. 10. Palpebral conjunctival papillae (moderate).
Source: reference.⁷

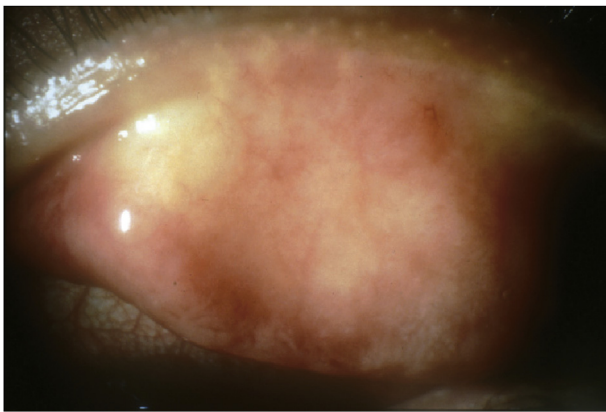


Fig. 8. Palpebral conjunctival swelling (moderate).
Source: reference.⁷

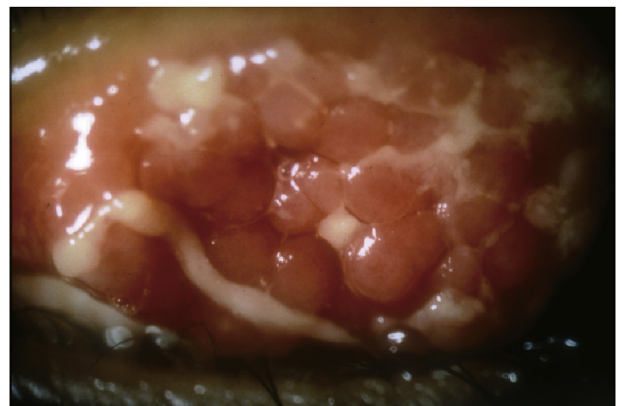


Fig. 11. Palpebral conjunctival giant papillae (severe).
Source: reference.⁷

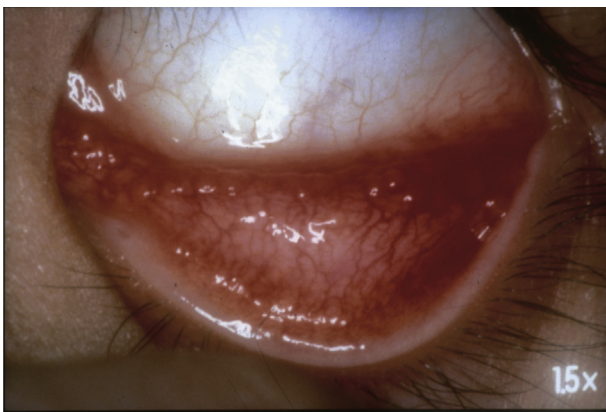


Fig. 9. Palpebral conjunctival follicles (severe).
Source: reference.⁷

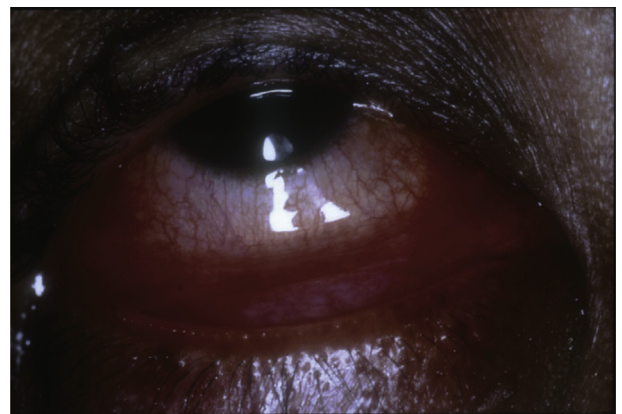


Fig. 12. Bulbar conjunctival hyperemia (severe).
Source: reference.⁷

uated according to the prominence range. In VKC, the papillar findings are also graded as severe.

5.3.2. Bulbar conjunctiva

The bulbar conjunctiva is evaluated according to hyperemia and chemosis. Since pathologic conditions are characterized by marked hyperemia (Fig. 12), the grade of “severe” hyperemia is defined as entire vascular dilation. Chemosis is evaluated according to its shape (Fig. 13).

5.3.3. Limbal conjunctiva

The Horner-Trantas dots is evaluated according to the number of the dots seen over the entire limbal region (Fig. 14), and the swelling is evaluated according to the range of the salmon pink swelling observed at the scleral side of the limbus (Fig. 15).

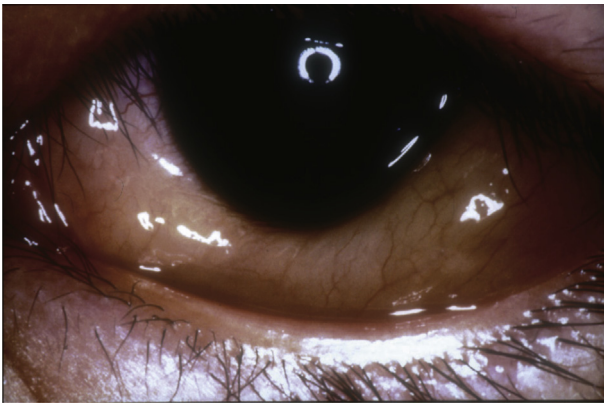


Fig. 13. Bulbar conjunctival edema (severe).
Source: reference.⁷

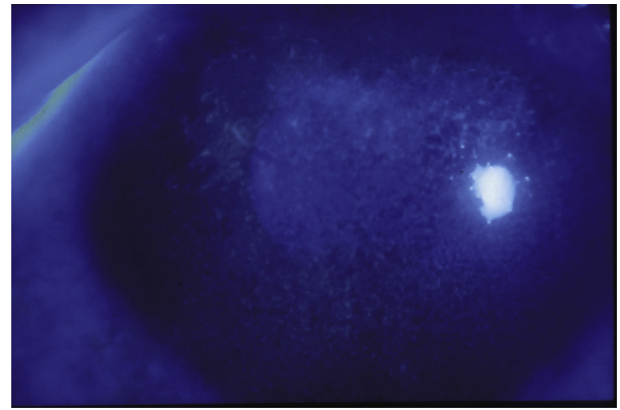


Fig. 16. Corneal epithelium disorder (moderate).
Source: reference.⁷



Fig. 14. Limbal conjunctiva Horner-Trantas dots (moderate).
Source: reference.⁷

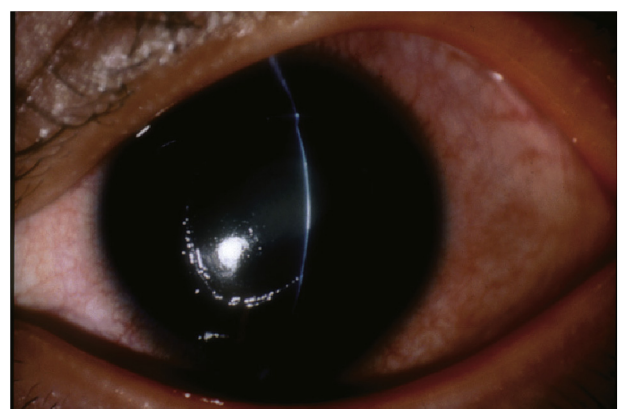


Fig. 17. Corneal epithelium disorder (severe).
Source: reference.⁷

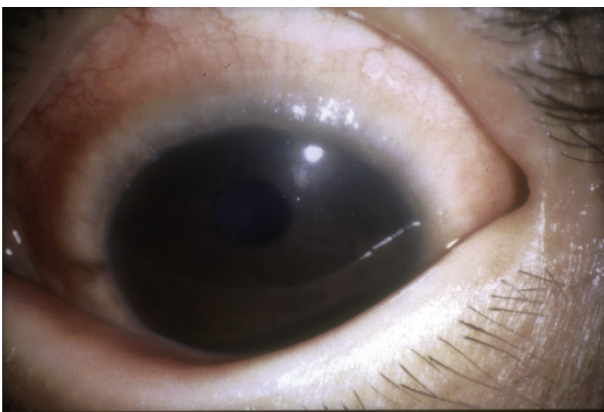


Fig. 15. Limbal conjunctival swelling (severe).
Source: reference.⁷

corneal epithelium disorder persists. Because the condition may persist even after the inflammation is alleviated, the presence or absence of defective epithelium was not included in the grading evaluation.

6. Diagnosis and differential diagnosis

In the diagnosis of allergic conjunctival diseases, it is required that type I allergic diathesis is present, along with subjective and objective symptoms accompanying allergic inflammation. The diagnosis is ensured by proving a type I allergic reaction in the conjunctiva (Table 2).

Table 2
Diagnostic criteria.

Clinical diagnosis (A only)	Clinical symptoms specific for allergic conjunctival diseases are present.
Quasi-definitive diagnosis (A + B)	In addition to the clinical diagnosis, positive results for serum antigen specific IgE antibody or skin reaction with presumed antigens.
Definitive diagnosis (A + B + C, A + C)	In addition to the clinical diagnosis, or quasi-definitive diagnosis, a positive result for eosinophils in the conjunctival smear.

A: Clinical symptoms are present. B: Type I allergic diathesis (systemic and local diathesis) are present. C: Type I allergic reaction in the conjunctiva is present.

5.3.4. Cornea (Fig. 16, 17)

The severity of the corneal epithelial defect is used as evaluation criteria. It is assumed in corneal disorders that superficial punctate keratitis is mildest and exfoliated superficial punctate keratitis is the next grade, and corneal erosion and shield ulcer follow in severity. Degenerated epithelium and mucin are deposited on the surface of the cornea and are observed as corneal plaque when

6.1. Clinical symptoms (A)

Frequent subjective symptoms are ocular itching, hyperemia, eye discharge, foreign body sensation, ocular pain, and photophobia. The ocular itching is the most common among all inflammatory symptoms accompanying type I allergic reactions, and is important as a basis for diagnosis.

Other important symptoms are hyperemia, eye discharge, and lacrimation, although those symptoms are not specific for allergic conjunctival diseases. Foreign body sensations, ocular pain, and photophobia are symptoms accompanying corneal lesions and indicate the severity of the inflammation rather than its diagnostic significance.

Giant papillae, limbal proliferation (limbal gelatinous hyperplasia, Horner-Trantas dot), and shield ulcer are important objective symptoms. Conjunctival edema and follicles, papillary hyperplasia, and corneal epithelial abrasion (corneal erosion and exfoliated superficial punctate keratitis) are “intermediately specific,” and conjunctival hyperemia and superficial punctate keratitis are “poorly specific.” However, the symptoms and findings that form the basis of diagnoses are slightly different among the diseases as shown in Figure 18.

6.2. Proof of type I allergic diathesis (B)

6.2.1. Systemic diathesis

Common methods to determine the presence or absence of allergic diathesis are those detecting serum antigen specific IgE antibody and skin reaction with a presumed antigen. In addition, an increase in serum total IgE antibody, the presence or absence of a familial history of allergic diseases, and complication of other allergic disease can be used as references.

6.2.2. Local diathesis

The proof can be made by increased total IgE antibody in lacrimal fluid.

6.3. Proof of type I allergic reaction (C)

To prove the presence of type I allergic reaction in the conjunctiva, it is necessary to prove to be positive for eosinophils in smears of eye discharge or ocular secretion.

6.4. Diagnosis of ACD

6.4.1. Seasonal allergic conjunctivitis (SAC)

A clinical diagnosis can be made by subjective symptoms including ocular itching, lacrimation, hyperemia and foreign body sensation, and objective symptoms including conjunctival hyperemia, conjunctival edema, and conjunctival follicles, which are found annually during the same season. The most common and important symptom of SAC is the ocular itching. Since the majority of SAC cases are conjunctivitis caused by pollen antigens, complicated symptoms of rhinitis are observed in 65–70% of cases. A positive test for serum antigen specific IgE antibody or a positive skin reaction, even in quasi-definitive diagnoses, makes it highly probable that a definite clinical diagnosis can be made. The serum total IgE antibody may be normal or mildly increased. The positive agreement rate in the measurement of the total IgE antibody in lacrimal fluid is about 70%.⁶ The exposure to a large amount of antigens may induce acute bulbar conjunctival edema.

6.4.2. Perennial allergic conjunctivitis (PAC)

A multi-seasonal or almost perennial ocular itching, lacrimation, hyperemia, and eye discharge are subjective symptoms of PAC and conjunctival hyperemia and papilla without proliferative change in the conjunctiva are objective symptoms. Most cases pass over chronically. The major antigens are house-dust-mite. Because it is very likely that the clinical symptoms are mild and characteristic objective symptoms are lacking, clinical diagnosis can be difficult in some cases, especially in elderly cases. Since the positive rate of eosinophils in the conjunctival smear is low, repetitive testing becomes necessary for the proof in some cases.

6.4.3. Atopic keratoconjunctivitis (AKC)

In AKC, the atopic dermatitis is complicated with facial lesions and conjunctivitis is perennially chronic with ocular itching, eye discharge, papillary hyperplasia, and corneal lesions. Proliferative lesions such as giant papillae and limbal lesions are present in some cases. Long-term chronic inflammation may result in fornix foreshortening and symblepharon. Increased total IgE antibodies in serum and lacrimal fluid and positive results of the serum antigen specific IgE antibody are found at high rates.

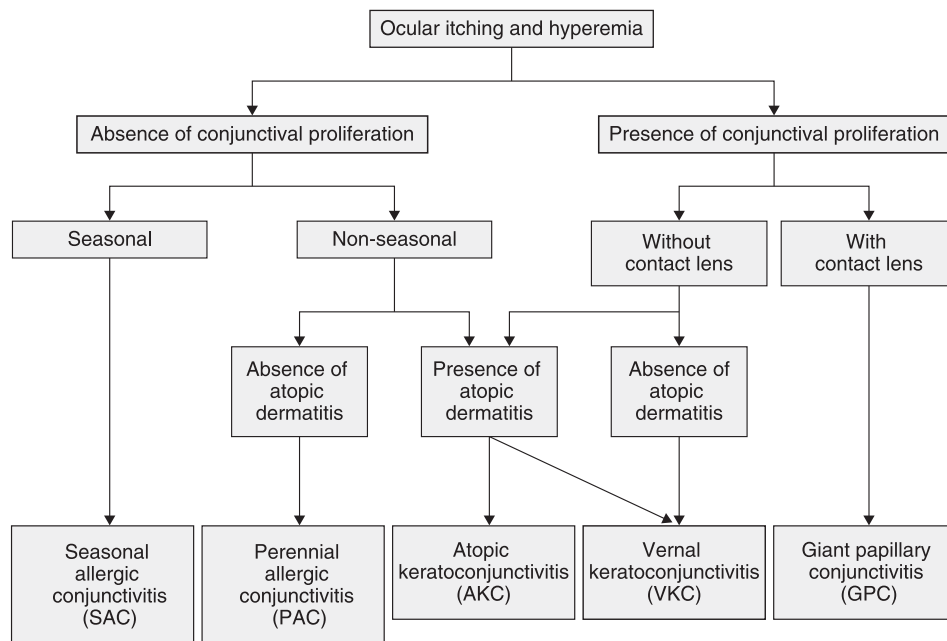


Fig. 18. Diagnostic flow-chart of allergic conjunctival diseases.

6.4.4. Vernal keratoconjunctivitis (VKC)

VKC is a severe allergic conjunctival disease with proliferative lesions in the conjunctiva. The proliferative lesion has giant papillae at the upper palpebral conjunctiva, limbal proliferation (limbal gelatinous hyperplasia and Horner-Trantas dots), and corneal lesions at high rates and easily becomes severe. Characteristic corneal lesions include exfoliated superficial punctate keratitis, shield ulcer (shield-shape ulcer), and corneal plaque. Clinical diagnosis is easy because the symptoms are characteristic. Major single-causative antigens are house-dust-mite, and the reaction with multiple kinds of antigens such as pollens and animal scurf occurs frequently. Increased total IgE antibodies in serum and lacrimal fluid and positive results for serum antigen specific IgE antibody are detected at high rates. In addition, a high positive rate of eosinophils in the conjunctival smear is found. Consequently, the definitive diagnosis is easy.

6.4.5. Giant papillary conjunctivitis (GPC)

In cases of contact lenses, ocular prosthesis, or surgical sutures, clinical diagnosis of GPC is made when ocular itching, foreign body sensations, and eye discharge are present and conjunctival hyperemia, conjunctival edema, and papillary hyperplasia are found. GPC induced by contact lenses is called contact lens related papillary conjunctivitis. Giant papillary conjunctivitis represents the most severe cases, which present with giant papillae of 1 mm or larger in diameter. The involvement of type I allergy is unknown in some cases and positive results for serum antigen specific IgE antibody are not frequent. A positive rate of eosinophils in GPC is rarer than that in other allergic conjunctival diseases.

6.5. Differential diagnosis

Infectious conjunctivitis such as viral, bacterial Chlamydia, non-inflammatory conjunctival folliculosis, and dry eye are considered as differential diagnosis.

7. Prophylaxis: self-care

7.1. 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 and it is necessary to take measures so that the daily activities of the patient will not be prevented by exposure to pollens.

7.2. Self care for allergic conjunctivitis

7.2.1. 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.

7.2.2. Contact lens insertion

During the pollen-flying period, it is useful to stop inserting contact lenses as much as possible, changing to glasses to avoid antigens.

7.2.3. Eye washing by artificial tear

Antigens flying into the ocular surface can be washed out by several drops of artificial tear. Because ordinary artificial tear contain preservatives, when instillation is repeated 4 or more times, an artificial tear without preservatives is recommended for safety. Since tap water reduces the stability of the layer of tears, frequent use of water for washing eyes should be avoided. Cup-type eye washing tools are not recommended because skin blurs around the eyes and antigens attaching to the skin touch the ocular surface.

8. Treatment: medical care

8.1. Fundamentals of treatment

Drug treatment is the preferred treatment for allergic conjunctival diseases. 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.

8.2. Antiallergic eye drops (Table 3)

Mast cell stabilizer inhibits the degranulation of mast cells and suppress release of mediators (e.g. histamine, leukotriene, thromboxane A₂), consequently, the early phase reaction to type I allergy is inhibited, and conjunctival local infiltration of inflammatory cells is curtailed, resulting in a reduction of the late phase reaction. Histamine H₁ receptor antagonists block histamine H₁ receptors, representative mediators released through the degranulation of mast cells, which results in suppression of hyperemia and ocular itching.

8.3. Steroids

8.3.1. Eye drops (Table 4)

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. Local side effects include elevation of intraocular pressure⁸ and induction of infection. It is necessary to measure the intraocular pressure regularly in children because the incidence of elevated intraocular pressure is high.⁹

8.3.2. 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.

8.3.3. Eye ointments (Table 5)

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

Table 3

Antiallergic eye drops.

Generic names	Product names	
Mediator antireleasers	Disodium cromoglicate	Intal® ophthalmic solution UD Intal® ophthalmic solution
	Amlexanox	Elics® ophthalmic solution
	Pemirolast potassium	Alegysal® ophthalmic solution Pemilaston® ophthalmic solution
	Tranilast	Rizaben® ophthalmic solution Tramelas® ophthalmic solution
	Ibudilast	Ketas® ophthalmic solution
	Acitazanolast hydrate	Zepelin® ophthalmic solution 0.1%
Histamine H ₁ receptor antagonists	Ketotifen fumarate	Zaditen® ophthalmic solution
	Levocabastine hydrochloride	Livostin® ophthalmic suspension 0.025%
	Olopatadine hydrochloride	Patanol® ophthalmic solution 0.1%
	Epinaestine hydrochloride	Alesion® ophthalmic solution 0.05%

Table 4

Steroid eye drops.

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

Table 5

Steroid eye ointments.

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

while sleeping. The same cautions as those in using steroid eye drops are necessary.

8.3.4. 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 less than 10 years.

8.4. Immunosuppressive eye drops (Table 6)

At present, 2 kinds of immunosuppressive eye drops (cyclosporine and tacrolimus) have been approved as treatment drugs for vernal keratoconjunctivitis. 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.¹⁰ Tacrolimus itself also has effects on steroid-resistant severe cases.¹¹

8.5. 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.

Table 6

Immunosuppressive eye drops.

Generic names	Product names
Cyclosporine	Papilock® mini ophthalmic solution 0.1%
Tacrolimus hydrate	Talymus® ophthalmic suspension 0.1%

8.6. Selection of treatment methods

8.6.1. Allergic conjunctivitis

The first option is antiallergic eye drops. A mast cell stabilizer and a histamine H1 receptor antagonist can be combined. During a period with severe symptoms, a steroid eye drop is combined. In seasonal allergic conjunctivitis, when the administration of an antiallergic eye drop is started about 2 weeks prior to the predicted day of the start of flying pollen or at the time when little symptoms appear, so that the symptoms decrease during the peak time of flying pollen.^{12,13}

8.6.2. Atopic keratoconjunctivitis (AKC)

When antiallergic eye drops alone are not sufficiently effective, a steroid eye drop is combined. At the same time, it is necessary to treat atopic blepharitis actively. When a steroid oral medicine is prescribed, the treatment should be conducted in cooperation with an internist and a dermatologist.

8.6.3. Vernal keratoconjunctivitis (VKC)

For moderate or more severe cases such that antiallergic eye drops alone are not sufficiently effective, an immunosuppressive eye drop is added. For severe cases when improvement cannot be achieved by 2 drugs, a steroid eye drop is added, and depending on the symptoms, a steroid oral medicine and sub-tarsal conjunctival steroid injection or surgical treatment should be attempted. When the symptoms are alleviated, the steroid eye drop should be changed to one with a lower titer or the number of the instillation should be gradually decreased, eventually stopping administration. Then, the treatment is conducted with an antiallergic eye drop and an immunosuppressive eye drop, and if the remission period becomes long, control is continued with the antiallergic eye drop only (Fig. 19).

8.6.4. Giant papillary conjunctivitis (GPC)

When a contact lens has a causative, the use of the contact lens is stopped as a rule, for the purpose of avoiding mechanical irritation and antigens. The first option is an antiallergic eye drop and in severe cases, a steroid eye drop is added. Because there have been frequent problems in the care of lenses, it is necessary to instruct patients in rub washing and changing of care tools.

9. Introductory points for medical specialists

For a case of conjunctivitis presenting with ocular itching as the major symptom, highly safe, anti-allergic ophthalmic eye drops can be prescribed as part of primary care by non-ophthalmologists. However, in cases where symptoms are not alleviated after 1–2 weeks of treatment, it is preferable for the physician to recommend the patient to visit an ophthalmology department. Additionally, symptoms resembling those of allergic conjunctivitis may have an etiology other than type I allergy, such as a bacterial or viral infection. In these cases, alternative investigations or treatments will be required in consultation with an ophthalmologist. When the therapeutic effects of anti-allergic eye drops alone are insufficient, steroid eye drops are administered in combination. However, steroid eye drops may cause side effects such as increased ocular pressure and exacerbation of ocular infections; hence, it is necessary for patients to undergo regular examinations by an ophthalmologist, which include ocular pressure measurements. In patients using contact lenses who have suspected allergic conjunctivitis, with symptoms such as severe ocular itching, hyperemia, and ocular discharge among others, as a rule, the contact lenses are removed prior to treatment. Although contact lenses may be worn when these symptoms are absent, it is necessary to carefully determine the use of contact lenses in consultation with a family ophthalmologist. On the other hand, owing to introduction of

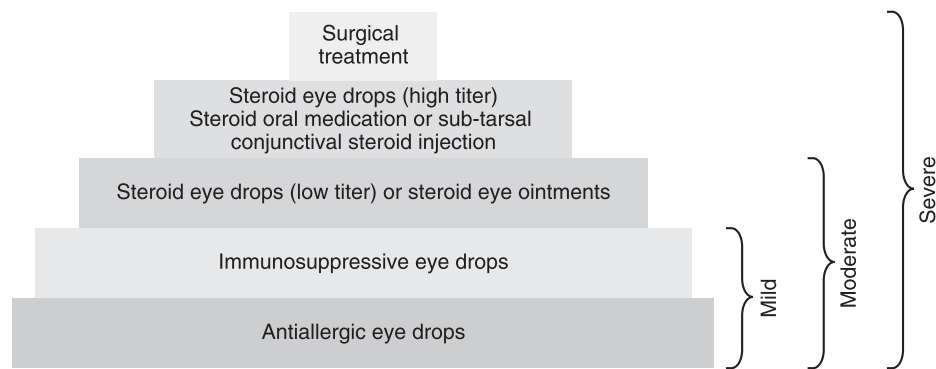


Fig. 19. Treatment of ACDs: proliferative (vernal keratoconjunctivitis).

immunosuppressive eye drops, symptoms of severe vernal keratoconjunctivitis and atopic keratoconjunctivitis can be alleviated in a short period, which enables treatment with decreased doses or discontinuation of combined steroid eye drops. For prescribing immunosuppressive eye drops, it is required for the ophthalmologist to examine the patient; therefore, in pediatric patients with symptoms of severe, complicated perennial allergic conjunctivitis or patients with atopic dermatitis, who may have suspected vernal keratoconjunctivitis or atopic keratoconjunctivitis, respectively, it is preferable for the physician to recommend that the patient be examined in an ophthalmology department.

Conflict of interest

Each of ET, JS, KF received lecture fees from Santen. KN received research funding from Santen. AF received lecture fees and research funding from Santen, Alcon Japan. HF received lecture fees from Santen, and research funding from White Medical. The rest of the authors have no conflict of interest.

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