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Invited Review Article

Executive summary: Japanese Guidelines for allergic conjunctival diseases 2021☆

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ABSTRACT

Allergic conjunctival disease (ACD) is an inflammatory disease of the conjunctiva that is mainly caused by type I hypersensitivity response to allergens and accompanied by subjective symptoms and other findings induced by antigens. ACD is classified as allergic conjunctivitis, atopic keratoconjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis. This article summarizes the third edition of the Japanese guidelines for allergic conjunctival diseases published in 2021 and outlines the diagnosis, pathogenesis, and treatment of ACD.

Since the introduction of immunosuppressive eye drops, the treatment strategies for severe ACDs have significantly changed. To clarify the recommended standard treatment protocols for ACD, the advantages and disadvantages of these treatments were assessed using clinical questions, with a focus on the use of steroids and immunosuppressive drugs. This knowledge will assist healthcare providers and patients in taking an active role in medical decision making.

1. Definition of allergic conjunctivitis disease

1.1. Definition

Allergic conjunctival disease (ACD) is defined as "an inflammatory disease of the conjunctiva that is mainly caused by type I hypersensitivity response to allergens and accompanied by subjective symptoms and other findings induced by antigens." ACD is diagnosed only when inflammatory changes occur in the conjunctiva and subjective symptoms, such as itching, foreign body sensation, seborrhea, and tears, develop. The mere presence of an allergic predisposition is not sufficient to determine an ACD.

1.2. Classification

ACDs are classified into several types according to the presence or absence of proliferative changes in the conjunctiva (proliferative changes in the conjunctiva refer to the papillary proliferation of the eyelid conjunctiva, including giant papillae, swelling, and bank-like elevation of the limbal conjunctiva), concomitant atopic dermatitis, and mechanical stimuli induced by foreign bodies, including contact lenses (Fig. 1A).[1]

☆ This article is based on the Japanese Guidelines for Allergic Conjunctival Diseases, 3rd edition, in Japanese published in 2021. Available at: https://www.nichigan.or.jp/member/journal/guideline/detail.html?itemid=429&dispmid=909.

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1.2.1. Allergic conjunctivitis (Fig. 1B)[1]

Allergic conjunctivitis (AC) is a non-proliferative disease. Seasonal allergic conjunctivitis (SAC) is defined as seasonal onset of symptoms. If the symptoms are perennial, they are called perennial allergic conjunctivitis (PAC). In PAC, exacerbations and remissions occur due to seasonal or climatic changes.

1.2.2. Atopic keratoconjunctivitis (Fig. 1C)[1]

Atopic keratoconjunctivitis (AKC) is a chronic allergic conjunctivitis that occurs in patients with atopic dermatitis involving the facial skin and is often accompanied by fibrosis of the conjunctiva, neovascularization, and opacity of the cornea. AKC is often associated with conjunctival fibrosis, corneal neovascularization, and corneal opacity. Although many patients with AKC do not experience proliferative changes, acute exacerbations may be accompanied by proliferative changes such as giant papillae.

1.2.3. Vernal keratoconjunctivitis (Fig. 1D)[1]

Vernal keratoconjunctivitis (VKC) is a proliferative ACD. A variety of corneal lesions, such as corneal epitheliopathy, corneal erosions, prolonged corneal epithelial defects, shield ulcers, and corneal plaques, are observed in VKC.

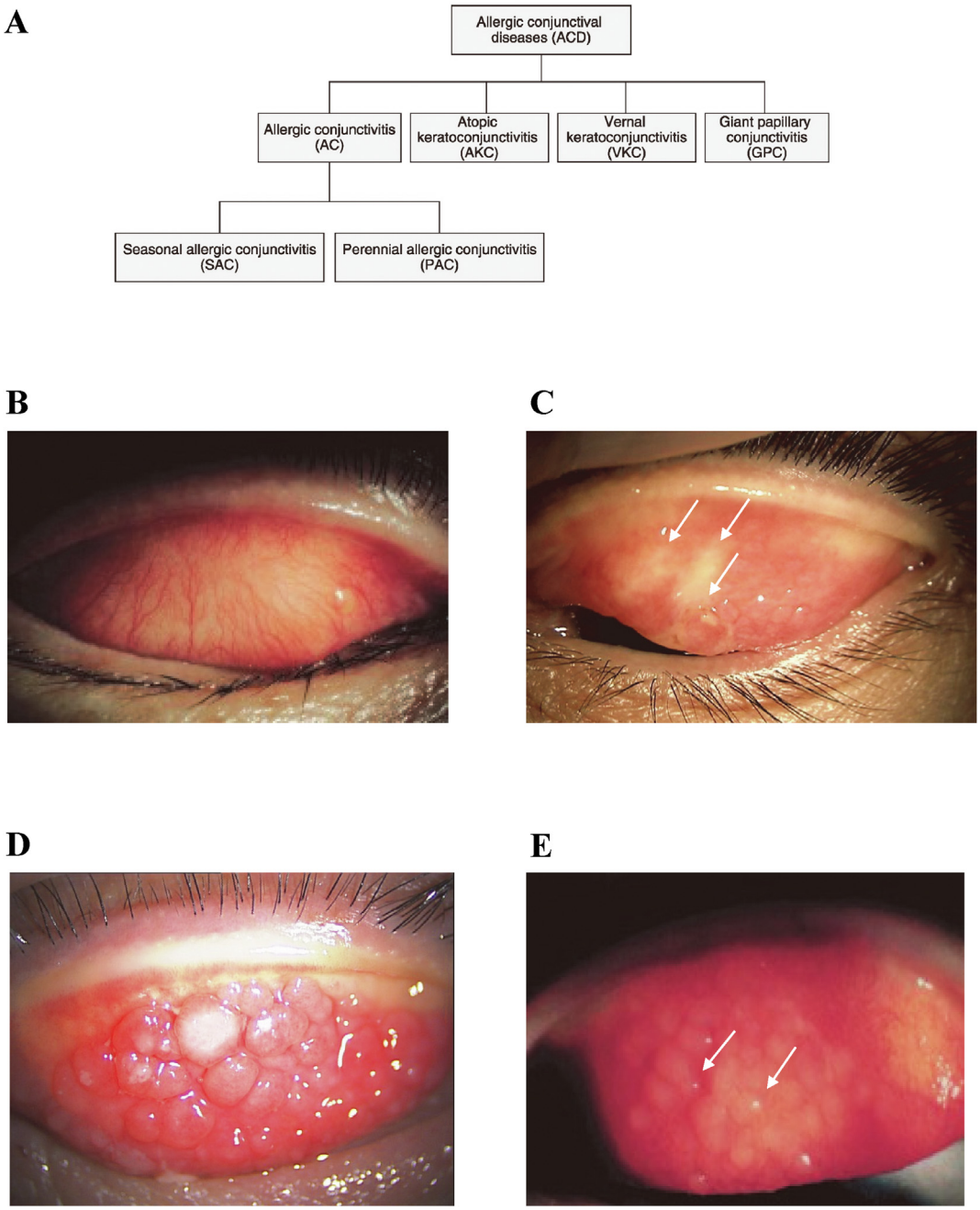

Fig. 1. **(A)** Classification of allergic conjunctival diseases.[1] Allergic conjunctival diseases are classified into 1) allergic conjunctivitis without proliferative changes, 2) AKC associated with atopic dermatitis, 3) VKC with proliferative changes, and 4) GPC caused by foreign body stimuli. Allergic conjunctivitis is subdivided into SAC and PAC according to the onset of symptoms. **(B)** Upper eyelid conjunctival findings in AC.[1] There is mild hyperemia and swelling. **(C)** Upper eyelid conjunctival findings in AKC.[1] There is hyperemia, opacity, and subconjunctival fibrosis (arrows). **(D)** Upper eyelid conjunctival findings in VKC.[1] Conjunctival hyperemia, swelling, discharge, and formation of giant papillae are seen. **(E)** Upper eyelid conjunctival findings of GPC.[1] Hyperemia and dome-shaped giant papillae (arrows) are seen.

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1.2.4. Giant papillary conjunctivitis (Fig. 1E)[1]

Giant papillary conjunctivitis (GPC) is conjunctivitis with proliferative papillary changes induced by mechanical stimuli, including use of contact lenses, prostheses, or surgical sutures. GPC is the most severe form of contact lens-related papillary conjunctivitis. The clinical picture of GPC is different from that of VKC: (1) the shape of the papillae differs; (2) in most cases, GPC is not accompanied by corneal lesions; and (3) GPC improves rapidly after removal of the cause.

2. Tests and diagnosis of allergic conjunctival disease

2.1. Allergy testing in the conjunctiva

The different clinical tests used to confirm the presence of type I allergic reactions in the conjunctiva include (1) identification of eosinophils in the conjunctiva, (2) measurement of total IgE antibodies in the tear sample, and (3) conjunctival allergen provocation test.

2.1.1. Identification of eosinophils in the conjunctiva

Eye discharge or secretions are smeared on a glass slide, stained with Hansel or Giemsa stain, and observed under an optical microscope. The sensitivity of conjunctival eosinophil test for detecting ACDs was 42.5%.[2] The sensitivity of this test was relatively high for VKC (75.0%). In contrast, the sensitivity of this test for SAC, PAC, GPC, and AKC remained low (SAC, 20.0%; PAC, 36.8%; AKC, 53.3%; and GPC, 33.3%).

2.1.2. Measurement of total IgE antibodies in tear samples

Patients with ACD show high total IgE levels in the tear fluid. The elevation of total IgE levels in the tear fluid can be detected using immunochromatography. The sensitivity of immunochromatography for detecting ACD was reported to be 72.2%.[2] The sensitivity was especially high for VKC (94.7%) and AKC (80.5%). By contrast, the sensitivities of this test for SAC, PAC, and GPC were 61.9%, 65.4%, and 75.0%, respectively. However, the test is semiquantitative and detects the total IgE level, not the antigen-specific IgE level.

2.1.3. Conjunctival allergen provocation test

This test evaluates the reaction to specific allergens such as itching or development of clinical symptoms after the topical application of antigens that cause IgE-mediated allergic reactions.[3] The conjunctival allergen provocation test (CAPT) has high sensitivity and specificity for the diagnosis of allergen sensitization, with 90% sensitivity and 100% specificity reported for PAC patients.[4] Before conducting CAPT, allergen sensitization tests, including skin prick tests or measurement of serum-specific IgE, are performed to identify the specific cause of disease exacerbation or anaphylaxis.

2.2. Systemic allergy testing

A systemic test reveals the presence of antigen-specific IgE antibodies. It has two main types: skin prick and serum allergen-specific IgE tests.

3. Clinical features and evaluation criteria

3.1. Subjective symptoms

The most common subjective symptoms of ACD are itching, foreign body sensation, and eye discharge. Itching is the most common characteristic symptom of ACD, but some patients complain of a foreign body sensation instead of itching. Foreign body sensations are frequently observed in patients with ACDs. In addition to perceiving mild itching as a foreign body sensation, the conjunctival papillae may come into contact with the cornea during blinking, resulting in a foreign body sensation. Eye discharge is secreted by the conjunctiva and consists mainly of water-soluble and non-water-soluble mucins. The cellular components include inflammatory cells that have leaked out from the blood vessels and detached or disintegrated the epithelium. In ACDs, lymphocytes and eosinophils comprise the majority of inflammatory cells, while neutrophils are scarce. It is often characterized by production of serous or mucous discharge.

3.2. Objective symptoms and evaluation criteria (Table 1)

3.2.1. Conjunctival hyperemia

Dilatation of conjunctival blood vessels is the most common finding in patients with ACDs (Fig. 2, 3).

3.2.2. Conjunctival swelling

It is caused by impaired circulation of the eyelid conjunctival vessels and lymphatic vessels and often occurs in the eyelid conjunctiva (Fig. 4).

3.2.3. Conjunctival follicles

These lymphatic follicles occur under the conjunctival epithelium of the lower eyelid (Fig. 5).

3.2.4. Conjunctival papillae

It is defined as the inflammatory proliferation of the epithelium, with thickening of the epithelium (Fig. 6). A network of blood vessels extending from the center is always present even in small papules. A papilla with a diameter of $\geq$1 mm is regarded as a giant papilla (Fig. 7).

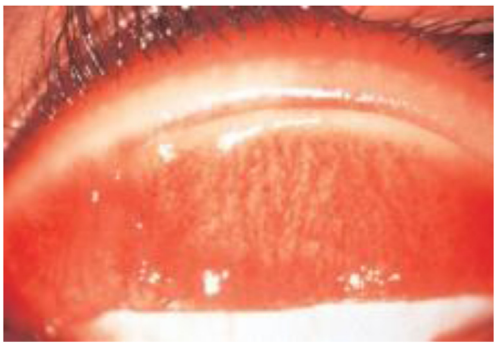

Fig. 2. Eyelid conjunctival hyperemia (severe).[1]

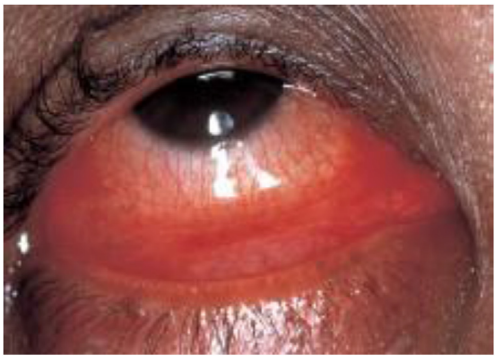

Fig. 3. Bulbar conjunctival hyperemia (severe).[1]

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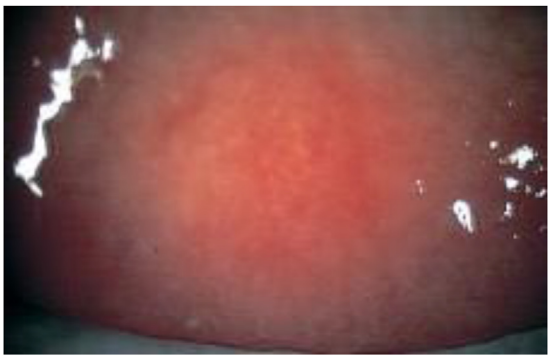

Fig. 4. Eyelid conjunctival swelling (severe).[1]

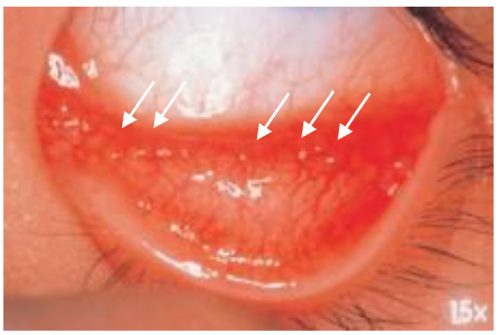

Fig. 5. Eyelid conjunctival Follicle (severe, Follicle: Arrow).[1]

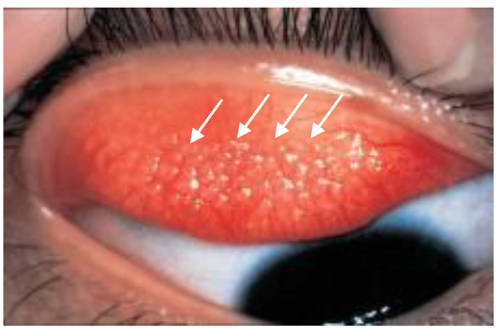

Fig. 6. Eyelid conjunctival papillae (severe, papillae: arrows).[1]

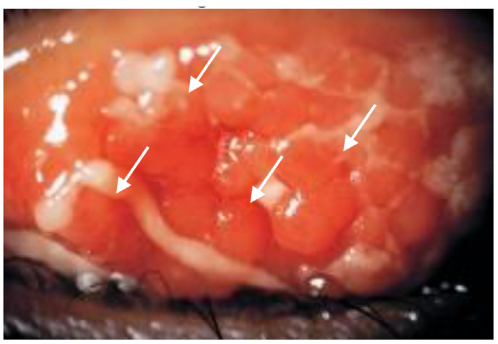

Fig. 7. Giant papilla of the tarsal conjunctiva (severe, giant papilla: arrow).[1]

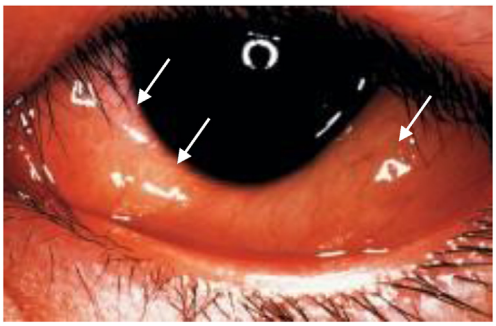

Fig. 8. Bulbar conjunctival edema (severe, edema: arrow).[1]

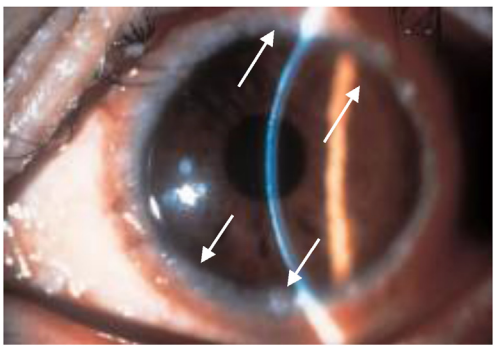

Fig. 9. Limbal Trantas dots (arrow, severe).[1]

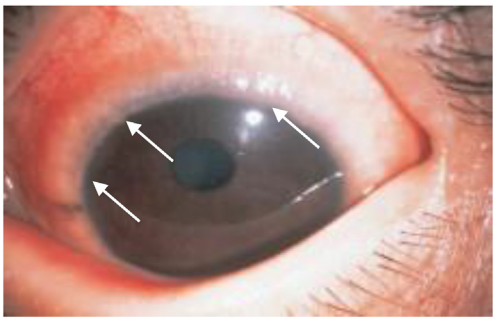

Fig. 10. Limbal swelling (arrow, severe).[1]

3.2.5. *Conjunctival edema*

It is often observed in the conjunctiva of the eye (Fig. 8). This is due to the leakage of plasma from dilated blood vessels and is a specific finding in patients with type I ocular allergy.

3.2.6. *Horner-Trantas dots*

Horner-Trantas dots are observed with limabal swelling (Fig. 9, 10). Horner-Trantas dots are small bumps caused by degeneration of the proliferating conjunctival epithelium with aggregation of eosinophils, which are specifically observed in individuals with allergic diseases.

3.2.7. *Corneal complications*

These complications include superficial punctate epithelial keratitis (partial loss of corneal epithelium), epithelial erosion, shield ulcer, or corneal plaque (Fig. 11). After intense inflammatory

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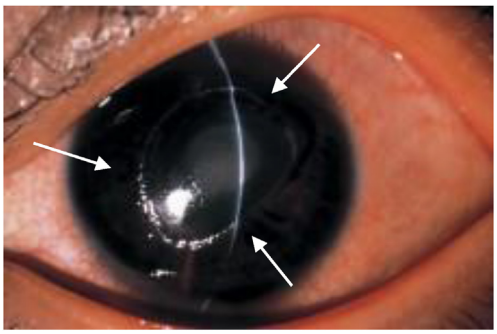

Fig. 11. Corneal epithelial damage (arrow, severe).[1]

responses, panni are formed with corneal neovascularization, or lipid deposition in the peripheral cornea may form pseudogerontoxons.

4. Diagnosis and differential diagnosis

4.1. Basis for diagnosis

ACD is diagnosed based on type I allergic predisposition, subjective symptoms associated with allergic inflammation, and other objective findings. A definitive diagnosis requires a type I allergic reaction in the conjunctiva. Clinical symptoms, predisposition to a type I allergy, and the presence of a localized type I allergic reaction in the eye (conjunctiva) are necessary for the diagnosis of ACD (Table 2). Definitive diagnosis is confirmed if all criteria are met or the patient developed clinical symptoms and tested positive for local type I allergy. A clinically definitive diagnosis is defined as the presence of clinical symptoms and a positive predisposition to type I allergy.

4.2. Clinical symptoms

The most common subjective symptoms are eye itching, hyperemia, ocular discharge, tearing, foreign body sensation, eye pain, and photophobia. Eye itching is the most common inflammatory symptom associated with type I allergic reactions and is an important basis for obtaining a diagnosis (Table 3). Among other symptoms, hyperemia, eye discharge, and tearing are also important, but are less specific. In general, eye discharge is present, but often mild and may be serous or mucopurulent. In VKC, yellow viscous eye discharge may be observed. Foreign body sensation, ocular pain, and photophobia are symptoms associated with corneal lesions and are used to determine the severity of disease.

Other findings such as giant papillae, limbal proliferation (thickening of the limbal conjunctiva with gelatinous appearance, also known as Horner-Trantas dots), and shield ulcers are

Table 1
Clinical evaluation criteria for allergic conjunctival diseases.

Tarsal conjunctiva	Hyperemia	None (−)	No manifestations
		Mild (+)	A few dilated blood vessels
		Moderate (++)	Multiple vasodilatation
		Severe (+++)	Not identifiable for individual vessels
	Conjunctival welling	None (−)	No manifestations
		Mild (+)	Slight swelling
		Moderate (++)	Diffuse thin swelling
		Severe (+++)	Diffuse swelling with opacity
	Follicle	None (−)	No manifestations
		Mild (+)	1 to 9 follicles
		Moderate (++)	10 to 19 follicles
		Severe (+++)	More than 20
	Papillae	None (−)	No manifestations
		Mild (+)	Diameter 0.1–0.2 mm
		Moderate (++)	0.3–0.5 mm in diameter
		Severe (+++)	Diameter 0.6 mm or more
	Giant papilla	None (−)	No manifestations
		Mild (+)	Papillae are flattened
		Moderate (++)	Elevated papillae within less than $^1/_2$ of the upper eyelid conjunctiva
		Severe (+++)	Elevated papillae over $^1/_2$ of the upper eyelid conjunctiva
Bulbar conjunctiva	Hyperemia	None (−)	No manifestations
		Mild (+)	A few dilated blood vessels
		Moderate (++)	Multiple vasodilation
		Severe (+++)	Diffuse vasodilation
	Edema	None (−)	No manifestations
		Mild (+)	Partial edema
		Moderate (++)	Diffuse, thin edema
		Severe (+++)	Swollen edema
Limbus	Trantas dot	None (−)	No manifestations
		Mild (+)	1 to 4 dots
		Moderate (++)	5 to 8 dots
		Severe (+++)	More than 9 dots
	Swelling	None (−)	No manifestations
		Mild (+)	Less than 1/3 of the circumference
		Moderate (++)	1/3–2/3 of the circumference
		Severe (+++)	More than 2/3 of the circumference
Cornea	Epithelial damage	None (−)	No manifestations
		Mild (+)	Superficial punctate epithelial keratitis
		Moderate (++)	Exfoliative punctate epithelial keratitis
		Severe (+++)	Shied ulcer

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Table 2
Diagnostic criteria.

Clinical diagnosis (A only)	Clinical symptoms characteristic of allergic conjunctival disease are present.
Clinically definitive diagnosis (A + B)	In addition to the clinical diagnosis, positive total IgE in tear fluid, positive serum antigen-specific IgE antibodies, or positive skin reaction consistent with the antigen.
Definitive diagnosis (A + B + C, A + C)	In addition to the above, eosinophils in conjunctival smear are positive.

A, Clinical symptoms are present; B, Type I allergy predisposition (systemic or local predisposition) is present; C, Type I allergic reaction in the conjunctiva.

Table 3
Specificity of clinical symptoms.

Specificity	Clinical symptoms (objective findings)	Subjective symptoms
High	Giant papillae, limbal proliferation, shield ulcer	Ocular pruritus
Moderate	Conjunctival edema, conjunctival follicle, papillary proliferation, corneal erosion, exfoliative superficial keratitis, corneal plaque	Ocular pruritus
Small	Conjunctival hyperemia, superficial punctate keratitis	Ocular pruritus, eye discharge, tearing, foreign body sensation, eye pain, photophobia

important for the diagnosis of VKC and AKC. Conjunctival edema, conjunctival follicles, papillary proliferation, and corneal epithelial exfoliation or macro erosion are rated as “medium specificity” for diagnosis, while conjunctival hyperemia and punctate superficial keratitis are rated as “low specificity” (Table 4).

4.3. Evidence of type I allergic predisposition

4.3.1. Systemic predisposition

Serum antigen-specific IgE levels and skin reactions to allergens are used to determine an allergic predisposition. The serum total IgE level, family history of allergic diseases, and other allergic diseases are also helpful.

4.3.2. Local predisposition

Positivity of total IgE in the tear fluid (immunochromatography of tear fluid, AllerWatch).[5,6]

4.4. Evidence of type I allergic reactions in the conjunctiva

Presence of eosinophil is determined by conjunctival smear.

4.5. Diagnosis of allergic conjunctival disease

A flowchart of the diagnosis of each disease is shown in Figure 12.

4.5.1. SAC

Subjective symptoms, such as eye itching, tearing, redness, and foreign body sensation, occur in a certain season. Conjunctival edema, conjunctival follicles, and conjunctival papillae can be used for the clinical diagnosis. The most common symptom was eye itching. In most cases, pollen conjunctivitis is caused by an overreaction to cedar and cypress pollen antigens. Other allergens included duckweed, timothy grass, Japanese white birch, mugwort, ragweed, and Japanese alder.[7] Allergic rhinitis was observed in 48% of patients.[7] A positive serum antigen-specific IgE or a positive skin reaction is sufficiently reliable for making a diagnosis. The serum total IgE level was normal or mildly increased, and the total IgE level in the tear fluid had a positive concordance rate of approximately 60%.[2]

4.5.2. PAC

Subjective symptoms such as eye itching, tearing, redness, and discharge occur throughout the year. Conjunctival follicles and papillae are present, but no proliferative changes are observed. House dust and mites are the most common antigens detected. In older patients, the clinical symptoms are often mild and lack characteristic findings. The positivity rate of smear testing for conjunctival eosinophilia is not high, and repeat testing may be necessary in some cases.

4.5.3. AKC

Conjunctivitis is perennial and chronic, and ocular pruritus, eye discharge, papillary proliferation, and corneal lesions are observed. Facial and eyelid skin lesions are often accompanied. Proliferative lesions are generally absent; however, giant papillae and limbal lesions may be present. Conjunctival shortening and symblepharon may occur in patients with chronic cases. The total IgE level in the serum and tear fluid increases, and the serum antigen-specific IgE test shows positive results. High levels of eosinophils are also observed in the conjunctiva.

Table 4
Key diagnostic evidence of diseases.

Disease	Key diagnostic evidence
Seasonal allergic conjunctivitis (SAC)	Seasonal, ocular pruritus, rhinitis symptoms, serum antigen-specific IgE antibody, skin reaction, conjunctival edema, conjunctival follicle
Perennial allergic conjunctivitis (PAC)	Perennial, ocular pruritus, eye discharge, eosinophils
Atopic keratoconjunctivitis (AKC)	Atopic dermatitis, eye discharge, corneal lesions, total IgE antibody, papillary proliferation, conjunctival shortening, symblepharon
Vernal keratoconjunctivitis (VKC)	Giant papillae, limbal proliferation, corneal lesions (Exfoliative superficial keratitis, shield ulcer, corneal plaque, ocular pain, eye discharge, hyperemia
Giant papillary conjunctivitis (GPC)	Wearing of contact lens or prosthesis, ocular pruritus, eye discharge, hyperemia

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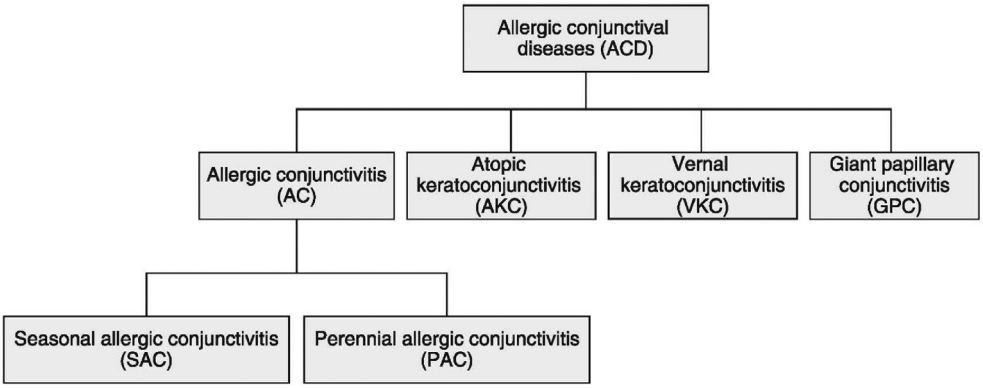

Fig. 12. Flowchart showing the process of obtaining a clinical diagnosis.

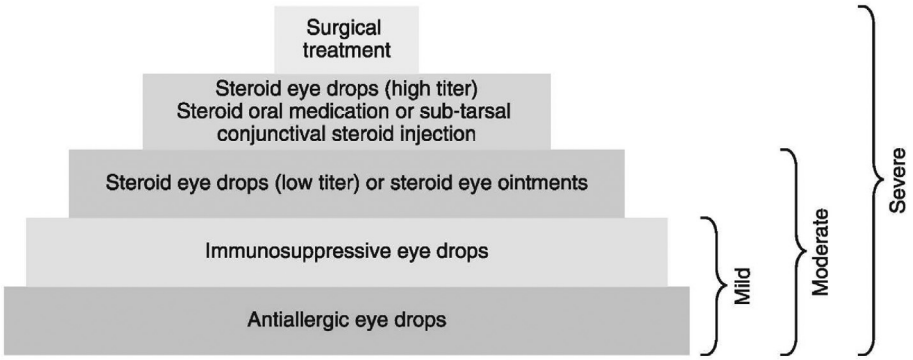

Fig. 13. Treatment of vernal keratoconjunctivitis based on the severity of disease.

4.5.4. VKC

VKC is a severe form of ACD that develops in childhood and characterized by presence of proliferative lesions on the upper eyelid conjunctiva and limbal lesions (giant papillae, limbal swelling, and Horner-Trantas dots). Corneal lesions (shield ulcers and corneal plaques) may also occur in those with severe cases. Corneal plaques may form due to the deposition of eosinophil-derived major basic proteins on the denuded Bowman's layer.[8] In patients with severe inflammation, including AKC, senile ring-like opacities (pseudogerontoxons) may occur. House dust and mites are the most common causative antigens, but other antigens, including pollens of cedar, cypress, timothy grass, duckweed, ragweed, mugwort, and animal dander, also induce the development of this disease. In addition to increased total IgE levels in the serum and tear fluid, serum antigen-specific IgE and conjunctival eosinophilia are also highly positive.

4.5.5. GPC

It is defined as the papillary proliferation of the upper eyelid conjunctiva caused by mechanical stimuli such as contact lenses, artificial eyes, and surgical sutures. It is characterized by ocular pruritus, foreign body sensation, eye discharge, conjunctival hyperemia, conjunctival edema, and papillary proliferation (>1 mm in diameter in severe cases). In some cases, the involvement of type I allergy is unclear, and serum antigen-specific IgE and eosinophil positivity rates are low.

4.6. Differential diagnosis

The differential diagnosis includes infectious conjunctival diseases, such as viral, bacterial, and chlamydial, and non-inflammatory conjunctival folliculosis and dry eyes.

4.6.1. Viral conjunctivitis

Conjunctival hyperemia, tearing, serous discharge, conjunctival follicles, and eyelid swelling are observed, and the symptoms are generally more severe than those of ACDs, with acute onset. The discharge appeared white and serous. Its onset is usually unilateral. Preauricular lymphadenopathy was also observed. The possible viruses that could cause this condition include adenovirus, herpes simplex virus, varicella zoster virus, enterovirus, and severe acute respiratory syndrome coronavirus 2.[9,10] Follicular conjunctivitis is difficult to differentiate from allergic conjunctivitis. In follicular conjunctivitis caused by adenovirus, a rapid diagnostic kit should be used to detect the viral antigens.

4.6.2. Bacterial conjunctivitis

Staphylococcus aureus, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are the common pathogens. Conjunctival hyperemia, conjunctival swelling, and eye discharge are observed despite the absence of conjunctival follicles. The eye discharge appears mucopurulent and yellow or yellow-green in color. Conjunctival smear staining shows the presence of polymorphonuclear leukocytes.

4.6.3. Chlamydial conjunctivitis

In adults, the disease presents as unilateral acute follicular conjunctivitis. It is characterized by the presence of large follicles in the forniceal conjunctiva of the lower eyelid. Marked conjunctival hyperemia, purulent eye discharge, and preauricular lymphadenopathy were observed. The diagnosis is confirmed by detection of chlamydial antigens, DNA, or intracellular inclusion bodies in conjunctival smears.

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4.6.4. Conjunctival folliculosis

It commonly develops in children. This is a clear miliary-sized follicle in the forniceal conjunctiva of the lower eyelid with no other pathological findings.

4.6.5. Dry eye

A decrease in the stability of the tear film layer causes ocular discomfort such as foreign body sensation, dryness, eye strain, and visual disturbance. It may be accompanied by hyperemia, papillary proliferation, and corneal and conjunctival epithelial damage. It is diagnosed by shortening the tear film breakup time. Dry eye is often associated with ACDs.

5. Treatment

Drug therapy is the mainstay treatment for ACDs. The first-line treatment is antiallergic drugs, which form the basis of treatment for ACD. Depending on the severity of the disease, corticosteroid (steroid) eye drops may be used. For refractory severe ACDs (AKC and VKC), immunosuppressive eye drops, oral steroids, subconjunctival injection of steroids, and surgical treatment such as resection of the tarsal conjunctiva, including papillae, should be considered.

5.1. Antiallergic drugs

5.1.1. Ophthalmic drugs (Table 5)

Mediator release inhibitors reduce the immediate phase of type I allergies by inhibiting the mast cell degranulation and the release of mediators, including histamine, leukotriene, or thromboxane A2; the delayed phase reactions are also reduced by inhibiting the local conjunctival infiltration of inflammatory cells. Histamine H1 receptor antagonists suppress hyperemia and itchiness by blocking the histamine H1 receptors.[11]

5.1.2. Oral medication

If antiallergic eye drops alone are not effective in patients with moderate or severe disease or in patients with allergic rhinitis, they are used in combination with other treatments.[12]

5.2. Steroids

Steroids have a broad anti-inflammatory effect by inhibiting the infiltration of inflammatory cells, such as mast cells, eosinophils, and lymphocytes; suppressing the production of inflammatory substances, such as cytokines and chemokines; and inhibiting vascular permeability. Steroids are available in the form of eye drops, oral medications, ointments, or injections.

5.2.1. Eye drops (Table 6)

When antiallergic eye drops alone are ineffective, steroid eye drops of a potency appropriate for the severity of inflammation should be used in combination. The topical ocular side effects include increased intraocular pressure, infection, and cataracts. In children, elevated intraocular pressure occurs more frequently.[13,14]

Table 5
Antiallergic eye drops.

Mediator release inhibitor	Pemirolast potassium Tranilast Ibudilast Acitazanolast hydrate
Histamine H1 receptor antagonist	Ketotifen fumarate Levocabastine hydrochloride Olopatadine hydrochloride Epinastine hydrochloride[11]

Table 6
Steroid eye drops.

Betamethasone phosphate sodium
Dexamethasone sodium phosphate
Dexamethasone metasulfobenzoate sodium
Fluorometholone

Hence, the intraocular pressure should be measured regularly. Therefore, the use of steroid eye drops in children should be carefully monitored.

5.2.2. Oral medications

Oral medications are used in children in cases where subconjunctival injection is difficult and in cases where corneal epithelial defects are observed. The duration of administration should be 1–2 weeks to avoid the development of side effects.

5.2.3. Ointment (Table 7)

Ophthalmic ointments are used when antiallergic eye drops alone are ineffective, steroid eye drops cannot be used, or blepharitis occurs. When patients with blepharitis, ophthalmic ointments should be applied after washing the face and rinsing the eye.[15] The same precautions should be taken when administering steroid eye drops.

5.2.4. Subconjunctival injection of steroid suspensions

In patients with refractory or severe cases, triamcinolone acetonide or betamethasone suspension is injected under the conjunctiva of the upper eyelid. Repeated use or use of this agent in children aged <10 years should be avoided, to avoid increasing the intraocular pressure.

5.3. Immunosuppressive eye drops

Currently, two types of immunosuppressive eye drops (cyclosporine and tacrolimus) are approved for the treatment of VKC. This is indicated for both children and adults. Immunosuppressive eye drops are as effective as or more effective than steroid eye drops.[16–19] Cyclosporine can be used in combination with antiallergic eye drops and steroid eye drops to reduce the dose of steroid eye drops. Tacrolimus alone is also effective in patients with severe cases who are refractory to steroids.[20–23]

5.4. Surgical treatment

5.4.1. Resection of conjunctival giant papilla

Resection of the conjunctival giant papilla may be performed in patients whose symptoms do not improve after receiving drug therapy and whose conjunctival papillary proliferation progresses and corneal epithelial damage worsens. Although an immediate therapeutic effect is achieved, recurrence may occur. With the recent introduction of immunosuppressive eye drops, the necessity of this procedure has been reduced.

5.4.2. Surgical removal of corneal plaque

Surgical removal may be indicated when epithelialization is not achieved owing to the presence of corneal plaques in the shield ulcer.[8]

Table 7
Steroid eye ointment.

Betamethasone phosphate sodium and fradiomycin sulfate
Dexamethasone methasulfobenzoate sodium
Methylprednisolone and fradiomycin sulfate
Prednisolone acetate

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5.5. Treatment options

5.5.1. Seasonal allergic conjunctivitis

The first-line treatment for SAC is antiallergic eye drops (mediator release inhibitors and histamine H1 receptor antagonists). If rhinitis symptoms are severe, antiallergic oral medications should be administered. Steroidal eye drops and non-steroidal anti-inflammatory drug (NSAID) eye drops may be used in combination when the symptoms are severe.[24,25] In addition, if antiallergic eye drops are initiated two weeks before pollen dispersal, the severity of symptoms that occurred at the peak of pollen dispersal could be reduced.[26]

5.5.2. Perennial allergic conjunctivitis

The first-line treatment for PAC is antiallergic eye drops. If antiallergic eye drops alone are ineffective, steroids or NSAID eye drops can be used in combination.[24,25] For patients who wear contact lenses or have dry eyes, preservative-free eye drops can be used.

5.5.3. Atopic keratoconjunctivitis

Antiallergic eye drops are the first-line treatment. In cases where antiallergic eye drops alone are ineffective, steroids and immunosuppressive eye drops should be used in combination. Atopic blepharitis must be reduced. Interleukin-4 receptor alpha-chain antibody (dupilumab), cyclosporine, or Janus kinase inhibitors may be administered as treatment for severe atopic dermatitis after referral to a dermatologist. Dupilumab is highly effective for atopic dermatitis and AKC.[27,28] However, a small number of patients may develop conjunctivitis,[29] which has been associated with the severity of atopic dermatitis and a history of conjunctivitis.[30] This can be commonly treated with topical steroids or antiallergic eye drops.[30]

5.5.4. Vernal keratoconjunctivitis (Fig. 13)

For patients with moderate or severe disease who do not respond well to antiallergic eye drops, additional immunosuppressive eye drops should be administered; in patients with severe cases who do not respond to treatment with two drugs, additional steroid eye drops, oral steroids, subconjunctival eyelid injections, or surgical treatment should be considered, depending on the symptoms. When symptoms improve, steroid eye drops with a lower potency are used, the frequency of drops is gradually reduced or discontinued, and the disease is treated with antiallergic and immunosuppressive eye drops. Proactive therapy may be indicated for long term control of the disease. Proactive therapy is a treatment in which the dosage of the medication is reduced while monitoring the symptoms to avoid relapse after adequate drug treatment, and eventually a small maintenance dose is continued. For example, if the clinical symptoms subside after receiving drug treatment twice daily, the dosage should be continued once a day or even twice a week to prevent recurrence.[31–33]

5.5.5. Giant papillary conjunctivitis

Causative mechanical stimuli, including contact lenses, artificial eyes, or sutures, should be alleviated. Wearing of contact lenses should be discontinued. Antiallergic eye drops are the first-line treatment; in patients with severe cases, steroid eye drops should be added. Since poor lens care may cause GPC, the patient should be instructed to avoid rubbing the contact lens and ensure regular replacement of care products. If the problem recurs, the contact lens should be frequently replaced, or disposable contact lenses should be used.

6. Systematic reviews and clinical questions

The strength of the body of evidence was assessed based on the methods described in the Minds Clinical Guidelines Manual 2017 (https://minds.jcqhc.or.jp/english or https://minds.jcqhc.or.jp/docs/minds/guideline/pdf/manual_all_2017.pdf [in Japanese]). The integration of the total body of evidence was based on qualitative integration, and quantitative integration was performed when appropriate. Eight criteria of Grading of Recommendations, Assessment, Development and Evaluation (GRADE) were used to assess the quality of evidence: risk of bias, indirectness of evidence, inconsistency of results, imprecision of results, risk of publication bias, effect size, dose−response gradient, and confounding effects. The quality of the evidence was rated on four levels: high, medium, low, and very low. Decisions on recommendations were based on the deliberations of the development group. Four GRADE criteria (evidence for outcomes, certainty about the balance of benefits and harms, values and preferences, and costs) were used to determine the recommendations. The RAND method was used to achieve consensus on the recommendations. The recommendation was considered strong when 80% or more of the panel endorsed the recommendation as “strong.”

CQ1 (Clinical Question 1). Are steroid eye drops effective in the treatment of seasonal allergic conjunctivitis and perennial allergic conjunctivitis?

Recommendation statement: Steroid eye drops are conditionally recommended for the treatment of seasonal allergic conjunctivitis and perennial allergic conjunctivitis. *Strength of recommendation:* Weakly recommended for use. *Level of evidence:* B. *Evaluation of evidence:* A PubMed search identified 17 articles for review.[24,34–49] The efficacy of steroid eye drops in allergic conjunctivitis has been reported in nine randomized controlled studies.[24,38–41,43,45,46,49] Of these randomized controlled studies, seven studies evaluated patients with the conjunctival hyperemia (four placebo-controlled comparative studies), two obtained the total scores of the objective findings, two evaluated patients with conjunctival edema, one obtained the total score of the subjective and objective findings, one evaluated patients with conjunctival papilla, one evaluated patients with conjunctival follicle, and one evaluated patients with eyelid edema. Among the clinical signs and symptoms, conjunctival hyperemia was evaluated in more than three studies and analyzed in a meta-analysis. The outcomes of these three studies showed that steroid eye drops were useful for treating conjunctival hyperemia (level of evidence: B). In addition, five of the six studies that could not be included in the meta-analysis showed that steroid eye drops were superior to placebo (level of evidence: A) or NSAID eye drops (level of evidence: B) in improving objective findings. These results supported the efficacy of steroid eye drops. Steroid eye drops can cause adverse effects, such as increased intraocular pressure (level of evidence: B), increased susceptibility to infection, steroid cataracts, and conjunctival vasodilation. They should only be used in patients with severe cases or in those who are not responsive to antiallergic eye drops. Hence, these patients should be adequately followed up by an ophthalmologist.

CQ2. Are steroid eye drops effective for vernal keratoconjunctivitis?

Recommendation statement: Steroid eye drops are conditionally recommended for the treatment of vernal keratoconjunctivitis. *Strength of recommendation:* Strongly recommended for use. *Level of evidence:* B. *Evaluation of evidence:* PubMed search yielded 16 articles for review.[50–65] Two randomized controlled trials (RCTs) comparing the efficacy of steroid eye drops in patients with VKC

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were retrieved.[64,65] In a 1983 study from West Africa, steroid eye drops (0.1% dexamethasone) were reported to significantly improve the clinical findings and symptoms compared with placebo.[65] In this study, 2% sodium cromoglycate eye drops, a mediator release inhibitor, were also reported to have similar therapeutic effects. A study conducted in 1995 reported the superior therapeutic efficacy of steroidal eye drops (0.1% betamethasone) compared with placebo,[64] and 0.1% betamethasone was considered more effective than NSAID (flurbiprofen 0.03%). A number of indirect evidences were obtained. For example, one study compared the effects of high-potency steroid eye drops on subjective symptoms, giant papillary tissue, and corneal epithelial damage in VKC patients treated with 0.1% cyclosporine eye drops and 0.1% tacrolimus eye drops. Although 0.1% cyclosporine eye drops were effective in improving the subjective symptoms and other findings of VKC, the symptoms worsened when high-potency steroid eye drops were switched to 0.1% cyclosporine eye drops. This finding indicates that high-potency steroid eye drops may be superior to 0.1% cyclosporine eye drops. Moreover, 0.1% tacrolimus eye drops are effective for treating VKC. High-potency steroid eye drops have been reported to be equally effective.

CQ3. Are steroid eye drops effective for atopic keratoconjunctivitis?

Recommendation statement: Steroid eye drops are conditionally recommended for atopic keratoconjunctivitis. *Strength of recommendation:* Strongly recommended for use. *Level of evidence:* B. *Evaluation of evidence:* The effectiveness of topical steroids for AKC is often examined in patients with severe ACDs including VKC. In contrast to VKC, only a few articles were related to AKC alone. One RCT compared the efficacy of steroidal eye drops and sodium cromoglycate eye drops in patients with AKC.[66] Results showed a marked superiority of steroid eye drops (medrysone) in improving itching, tearing, hyperemia, and superficial punctate keratitis scores. In AKC, steroid eye drops are used as the baseline standard of care. In a systematic review examining the efficacy of cyclosporine eye drops in AKC, steroid eye drops were used as the control.[67] Observed non-inferiority of steroid eye drop indicates indirect evidence.

CQ4. Are cyclosporine eye drops effective for vernal keratoconjunctivitis and atopic keratoconjunctivitis?

Recommendation statement: Cyclosporine eye drops are conditionally recommended for the treatment of vernal and atopic keratoconjunctivitis. *Strength of recommendation:* Weakly recommended for use. *Level of evidence:* B. *Evaluation of evidence:* For CQ4, a PubMed search yielded 23 studies.[55,67–88] Eight randomized controlled studies were included in this analysis.[71,75,76,80,86,89–91] The reported concentrations of cyclosporine eye drops ranged from 0.05% to 2%. Conjunctival papillae of the upper eyelid (giant papillae of the upper eyelid) and corneal epithelial damage were assessed in this meta-analysis. Cyclosporine eye drops showed significant therapeutic effects. By contrast, the heterogeneity (I^2) was high, at 89% and 88%, respectively. In particular, the therapeutic effects of cyclosporine eye drops were reported to be strong in studies that used a 2% concentration. The therapeutic effect was generally concentration dependent (dose–response gradient), and the therapeutic effect was consistently observed, although it was not always strong at low concentrations (level of evidence: B). The adverse events included eyelid and corneal herpesvirus infection and corneal bacterial infection, but these events rarely occur and have not been reported in randomized controlled studies. In summary, cyclosporine has a moderate therapeutic effect, does not increase intraocular pressure, and has no significant adverse effects compared with steroid eye drops. However, as its formulation is more expensive compared with that of steroid eye drops, its benefit is diminished.

CQ5. Are cyclosporine eye drops more effective than steroid eye drops for vernal keratoconjunctivitis and atopic keratoconjunctivitis?

Recommendation statement: Cyclosporine eye drops are conditionally recommended over steroid eye drops for vernal and atopic keratoconjunctivitis. *Strength of recommendation:* Weakly recommended for use. *Level of evidence:* C. *Evidence evaluation of evidence:* The PubMed search yielded 33 articles.[17,55,59,62,67,68,70–72,74–76,79–81,83,85,86,89–102] Two randomized controlled studies were included in the analysis.[55,59] One study compared 2% cyclosporine eye drops with high-potency steroid eye drops (dexamethasone) (n = 182/group).[59] Both treatments showed improvement in papillary scores, however, no significant difference was observed. For corneal epithelial damage, sufficient therapeutic effect was not observed in both groups. The 2% cyclosporine eye drops may be as effective as the high-potency steroid eye drops. However, 0.05% cyclosporine eye drops may not be comparatively effective. One study examined the effect of concomitant use of 0.05% cyclosporine eye drops with steroid eye drops. For steroid dependent AKC and VKC patients, addition of 0.05% cyclosporine eye drops did not improve therapeutic effect of steroid eyes drops.[55] Therapeutic effects have been consistently observed (level of evidence: C), and the side effects did not significantly increase compared with that of steroids. Given that the difference in the efficacy of cyclosporine and steroid eye drops is not significant, the cost of the formulation and the presence or absence of an increase in intraocular pressure are the primary criteria for selecting the preferred eye drops.

CQ6. Is the combination of cyclosporine eye drops and steroid eye drops effective for vernal keratoconjunctivitis and atopic keratoconjunctivitis?

Recommendation statement: In vernal keratoconjunctivitis and atopic keratoconjunctivitis, combination therapy with cyclosporine and steroid eye drops is conditionally recommended for patients with conjunctival proliferative changes. *Strength of recommendation:* Weakly recommended for use in combination. *Strength of evidence:* C (weak). *Evaluation of evidence:* No randomized controlled studies have evaluated the clinical findings and safety of cyclosporine and steroid eye drops when used as combination treatment. Two articles reporting the results of a nationwide post-marketing survey of cyclosporine eye drops[82,103] and two observational studies on cyclosporine eye drop treatment for VKC/AKC were used as bases for evaluating these agents.[96,104] These studies showed that combination therapy reduced the subjective symptoms and clinical scores in patients with VKC/AKC, including those on steroid eye drops, and that continued treatment increases the number of patients who can be weaned off steroid treatment. On the contrary, some patients experience difficulty in withdrawing from steroid treatment or relapse after withdrawal. This finding suggests that patients with VKC/AKC treated with cyclosporine eye drops can be classified according to the severity of the disease. These include patients who can be treated with cyclosporine alone, those requiring combination therapy, and those who are resistant to combination therapy.

CQ7. Are tacrolimus eye drops effective for vernal keratoconjunctivitis and atopic conjunctivitis?

Recommendation statement: Tacrolimus eye drops can improve the epithelial damage and giant papillae in patients with vernal keratoconjunctivitis and atopic keratoconjunctivitis and are recommended for the treatment of these conditions. *Strength of*

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recommendation: Strongly recommended for use. *Strength of evidence:* A. *Evaluation of evidence:* PubMed searches yielded 11 studies.[20–23,42,62,63,96,105–108] Two randomized controlled studies were conducted. One study examined both VKC and AKC,[42] while another examined VKC.[63] A meta-analysis of epithelial damage and giant papillae demonstrated the usefulness of tacrolimus eye drops. The incidence of complications such as infections and eye irritation was low and not significant. We also evaluated the findings of nationwide post-marketing surveys of tacrolimus ophthalmic products as observational studies with a large sample size.[21–23] In these studies, the strong therapeutic effects of VKC and AKC on giant papillae and corneal findings have been reported. However, many patients can be weaned off steroid eye drops but with continued tacrolimus eye drop treatment, suggesting that the drug may be particularly effective for patients who are either refractory to steroids or respond to steroids. The characteristic side effect is eye irritation.[42,63] However, this side effect has no impact on patients' compliance, and its influence on the treatment effect seems to be negligible. As the drug is more expensive than steroid eye drops, the cost of long-term use remains a concern.

CQ8. Are tacrolimus eye drops more effective than steroid eye drops for vernal keratoconjunctivitis and atopic keratoconjunctivitis?

Recommendation statement: Tacrolimus eye drops are recommended over steroids for the treatment of vernal and atopic keratoconjunctivitis. *Strength of recommendation:* Weakly recommended for use. *Strength of evidence:* B. *Evaluation of evidence:* PubMed search identified eight relevant studies for review.[21–23,42,62,63,105,106] One double-masked crossover study involving AKC patients compared the efficacy of topical administration of 0.1% tacrolimus ointment with that of 0.05% clobetasone ointment in patients with conjunctivitis, keratitis, and skin.[115)] The eyelid skin score was significantly lower in the tacrolimus group compared with that in the clobetasone group ($P = 0.05$); meanwhile, all other clinical scores were lower in the tacrolimus group but were not considered significant. Both groups did not exhibit an increase in intraocular pressure or develop ocular infection. Because the drugs used in the study had different specifications and were applied in the eyelid, the results should be interpreted with caution. We also evaluated the results of a nationwide post-marketing survey of tacrolimus eye drops.[21–23] The data showed that switching from steroidal eye drops significantly improved the giant papillae and corneal findings and that many patients were able to wean off steroidal eye drops but continued to use tacrolimus eye drop.

CQ9. Is the combination of tacrolimus eye drops and steroid eye drops useful in the treatment of vernal keratoconjunctivitis and atopic keratoconjunctivitis?

Recommendation statement: In vernal keratoconjunctivitis and atopic keratoconjunctivitis, combination therapy with tacrolimus and steroid eye drops is conditionally recommended for patients who demonstrated severe conjunctival proliferative changes. *Strength of recommendation:* Weakly recommended for use in combination. *Strength of evidence:* C (weak). *Evaluation of evidence:* No randomized controlled study has evaluated the efficacy of tacrolimus ophthalmic drops and steroid eye drops as combination treatment. In studies that included patients with concomitant use of steroid eye drops,[21,23] the clinical score significantly decreased 1 month after treatment, and the proportion of patients who required concomitant use of steroid eye drops decreased. These results indicate that tacrolimus eye drops can be used when steroid eye drops are tapered or discontinued. In a study that did not include patients treated with concomitant steroid eye drops, the clinical score decreased significantly in the first month after treatment.[109] Thus, the necessity for the concomitant use of steroid eye drops remains unclear. Data from a post-marketing nationwide survey using a generalized linear mixed-effects model showed similar results regarding the effect of the concomitant use of steroid eye drops as treatment for corneal damage.[22] In addition, the results of a study using generalized estimating equations also confirmed that the concomitant use of steroid eye drops had no appreciable effect on corneal damage, although some effects were observed in the overall clinical score.[23] When further evaluation was performed to confirm whether tacrolimus with or without topical steroids has a similar treatment effect, results showed that topical steroids should be avoided due to the possible occurrence of side effects. Combination therapy showed better therapeutic effects compared with single-agent therapy. However, the patients should be monitored for any undesirable effects. Considering that the evidence for both benefits and harms is insufficient, combination therapy with steroid eye drops should not be used for a long period of time. In patients who are refractory to combination therapy with steroid eye drops, alternative conjunctive therapy including subconjunctival steroid injection, supratarsal injection of triamcinolone, or oral steroids should be considered.

Conflict of interest

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