

REVIEW

Atopic keratoconjunctivitis: A review

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Atopic keratoconjunctivitis is a chronic noninfectious inflammatory condition and is one of the most severe ocular complications associated with atopic dermatitis. It requires prompt and effective treatment to prevent permanent vision loss. Complications of atopic keratoconjunctivitis include cataracts, keratoconus, infectious keratitis, blepharitis, tear dysfunction, and steroid-induced glaucoma. All treatment for atopic keratoconjunctivitis should be managed in conjunction with an ophthalmologist, and immediate referral is indicated when there is moderate to severe irritation, increased redness, discharge, or any visual symptoms. Treatment options include a combination of mast cell inhibitors, antihistamines, corticosteroids, and calcineurin inhibitors. (J Am Acad Dermatol 10.1016/j.jaad.2013.10.036.)

Key words: atopic dermatitis; atopic keratoconjunctivitis; conjunctiva; cornea; keratoconus; ocular; sight threatening.

Atopic dermatitis (AD) is a significant cause of ocular morbidity, with eye or eyelid involvement occurring in 20% to 43% of patients.¹⁻⁴ The most severe ocular complication is atopic keratoconjunctivitis (AKC), which was first described by Hogan in 1953¹⁻⁵ as keratoconjunctivitis in patients with AD.^{2,6,7} According to Guglielmetti et al,⁴ it should be redefined as follows: AKC is a chronic, noninfectious inflammatory condition affecting patients with AD at any point during their disease, independent of cutaneous disease severity. AKC is likely more common than previously believed¹ and is a potentially blinding condition if not treated early.^{4,5,7-9}

The data in the following literature review are evaluated according to the grading scheme in the modified Academy of Ophthalmology Preferred Practices guidelines, which evaluates clinical studies based on study design, control, and randomization and evaluates the basic science studies based on the level of publication.

IMMUNOPATHOPHYSIOLOGY

Atopic dermatitis

Genetic predisposition and immune system dysfunction both contribute to the development of AD. Filaggrin mutations, which are common in AD, increase susceptibility to bacterial infections and loss of moisture from the skin.¹⁰ In addition to the genetic

Abbreviations used:

AD:	atopic dermatitis
AKC:	atopic keratoconjunctivitis
IFN:	interferon
IL:	interleukin
KCN:	keratoconus
SAC:	seasonal allergic conjunctivitis
Th:	T-helper
VKC:	vernal keratoconjunctivitis

component, immune dysregulation in response to environmental allergens is a driving force in AD. In the acute phase, Langerhans cells present allergens and autoantigens to T cells via major histocompatibility complex (MHC) molecules. The activated T cells secrete prostaglandin E2 and interleukin (IL)-10 directing T-cell differentiation toward a predominantly T-helper (Th)2 response, characterized by IL-4, IL-5, and IL-13 overexpression.¹¹ In the chronic phase, elevated levels of eosinophils lead to overproduction of IL-12, which induces a transition to Th1 differentiation with interferon (IFN)- γ production.^{4,10,12}

Atopic keratoconjunctivitis

Allergic conjunctival disease may present as 3 distinct clinical entities: AKC, vernal keratoconjunctivitis (VKC), and seasonal allergic conjunctivitis

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(SAC), with AKC being the most severe form and SAC the least severe. The major cellular lines in AKC are mast cells, eosinophils, basophils, and T cells.^{4,6,12} As indicated by the elevated tear levels of IFN- γ , tumor necrosis factor- α , IL-2, IL-4, IL-5, and IL-10, AKC can be attributed to a combination of Th1 and Th2 responses (Th1 more prominent than Th2).^{1,4,6,12,13} Studies of in situ hybridization of ocular tissue by Calder et al⁶ and Bielory¹⁴ demonstrated elevated IL-2,¹⁴ IL-3, IL-4, and IL-5 messenger RNA expression.^{6,14} Patients with AKC exhibit higher levels of IL-8 and regulation of activation, normal T cell expressed and secreted, chemoattractants for other leukocytes in the conjunctival epithelium.^{4,13,15} IL-33, a Th2 cytokine that promotes IgE isotype switching and eosinophil infiltration, is significantly expressed in vivo in the epithelium and vascular endothelium of giant papillae of AKC conjunctival tissues when compared with controls.^{4,16}

Many inflammatory cytokines and chemokines are elevated in the tears of patients with AKC. One study demonstrated higher levels of IL-4 in the tears of patients with AKC compared with patients with VKC, patients with SAC, and control subjects.¹⁷ In a similar study, Uchio et al¹⁸ found higher levels of IL-4 in the tears of patients with AKC compared with patients with VKC. The tear levels of IL-4 correlate with the severity of AD but not AKC.^{17,18} Neither IL-2 nor IFN- γ tear levels appear to correlate with the severity of AKC.^{7,12} In contrast, tear levels of IL-5, a Th2 cytokine that activates and maintains eosinophils, have been shown to correlate with AKC disease severity.¹⁸

Eosinophil levels are elevated in the conjunctiva of patients with allergic eye disease.^{4,5,7} However, it is the level of activated eosinophils rather than the absolute number of eosinophils that is important in AKC.^{4,6} The activated eosinophils release gelatinase B, major basic protein, and eosinophil cationic protein, which may contribute to the corneal complications of AKC.^{4,7} Conjunctival fibroblasts appear to be another source of chemokines. In vitro studies of conjunctival fibroblasts exposed to tumor necrosis factor- α or a combination of tumor necrosis factor- α and IL-4 or IL-13 showed up-regulation and production of eotaxin, monocyte chemoattractant protein-1, and regulation of activation, normal T cell expressed and

secreted.^{6,12} Tear levels of eotaxin 1 correlate with severity of AKC.⁴

CLINICAL FINDINGS

AKC typically begins in the late teens and early 20s, although it has been reported as early as 7 years of age,^{5,9} and can persist into the fourth and fifth decades of life, with a peak incidence between 30 and 50 years old.^{1,4,5,14} It is usually perennial, but can be associated with seasonal exacerbations.^{1,4,5,19} Although only 20% to 43% of patients with AD have ocular involvement, AKC is associated with AD in 95% of cases.^{1,2,4}

Symptoms

The symptoms of AKC include itching, tearing, and burning of the eyes.^{1,4,14}

Patients typically present with chronic, rather than seasonal symptoms, including pain, redness, and blurred vision.^{1,4,20,21}

Signs

Eyelids. Patients with AKC may present with severe eczema of the eyelids and periorbital skin, both of which are areas commonly involved in AD.^{1,2,4} When associated with hyperpigmentation, this sign is known as “panda eyes.”⁴ Dennie-Morgan lines, which are infraorbital linear lid creases secondary to edema and thickening of the lid, may also be seen in AKC.^{1,14} When AD involves the eyelids (Fig 1), both anterior (secondary to staphylococcal disease) and posterior (secondary to structural changes and obstruction of meibomian gland orifices) blepharitis can be seen along the lid margin, and excess tear production with anterior migration of the tear meniscus can result in maceration of the skin.^{1,4,19,21}

Conjunctiva. By definition, AKC always includes chronic inflammation of the conjunctiva. Conjunctival involvement is bilateral, characterized by thickening and hyperemia.^{1,2,5,7,8,20} There is papillary hypertrophy of the upper and lower tarsal conjunctiva with a predilection for the lower tarsal conjunctiva^{1,2,14} (Figs 2 and 3). Foreshortening of the inferior fornix and less often the medial and lateral fornices is seen in AKC.^{4,14,21} Limbal Horner-Trantas dots, although rare, may occur transiently during exacerbation^{1,2,4,14} (Fig 4).

Cornea. In addition to chronic exposure to inflammatory mediators, trauma from thickened,

CAPSULE SUMMARY

- Atopic keratoconjunctivitis is a severe ocular complication of atopic dermatitis.
- Prompt recognition and treatment is essential to prevent blindness.
- Immediate referral to an ophthalmologist is indicated for moderate to severe ocular irritation, erythema, discharge, and visual symptoms.



Fig 1. Atopic dermatitis. Blepharitis with erythema, lichenification, hyperpigmentation, and secondary pustules of the eyelids. Photographed with a standard digital camera.

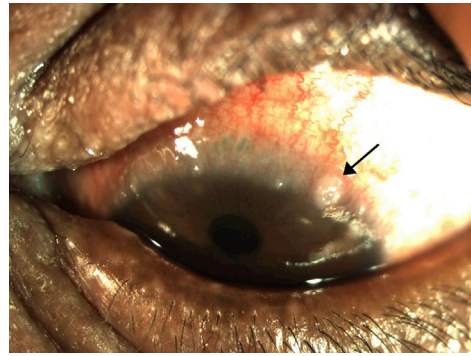


Fig 4. Atopic keratoconjunctivitis (AKC). Horner-Trantas dots along the superior limbus in AKC. Photographed with a slit-lamp biomicroscopy camera.

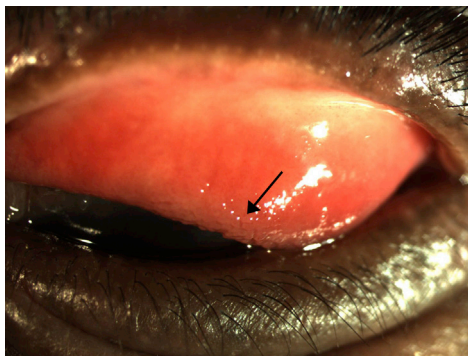


Fig 2. Atopic keratoconjunctivitis. Severe papillary reaction and thickening in the superior tarsal conjunctiva. Photographed with a slit-lamp biomicroscopy camera.

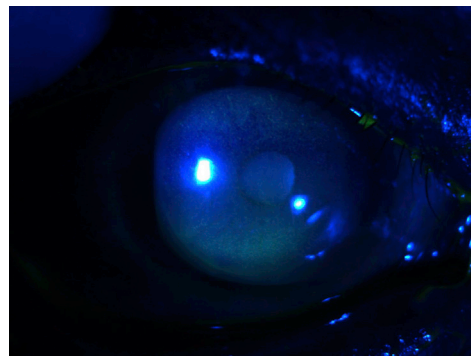


Fig 5. Atopic keratoconjunctivitis. Fluorescein staining showing diffuse superficial punctate keratopathy. Photographed with a slit-lamp biomicroscopy camera.



Fig 3. Atopic keratoconjunctivitis. Improvement of papillary reaction in the superior tarsal conjunctiva after treatment with tacrolimus 0.03% ointment. The patient applied tacrolimus 0.03% ointment twice a day to the eyelid margins. Photographed with a slit-lamp biomicroscopy camera.

inflamed tarsal conjunctiva and irregular lid margins can lead to both superficial punctate keratopathy and punctate corneal erosions^{2,4} (Fig 5). With time the corneal involvement can progress to frank

erosion, ulceration, and the formation of mucous plaques and epithelial filaments.^{1,2,4,5} Corneal scarring and neovascularization from persistent inflammation can lead to vision loss.^{1,2,5,14,19} In a study of 20 patients with 3 or more years of follow-up, Power et al⁵ found that 70% of patients with AKC developed significant keratopathy, including corneal neovascularization in 60%, fornix foreshortening in 25%, and symblepharon (tarsal conjunctival adhesions) in 20%, with more than 50% requiring penetrating keratoplasty (corneal transplantation).

Tear dysfunction. Atopy can be associated with meibomian gland dysfunction, tear film instability, goblet cell loss, and conjunctival squamous metaplasia.^{1,12,17} Hu et al¹⁷ found tear film break-up time to be decreased in patients with AKC. This study also found higher degrees of squamous metaplasia and lower goblet cell density in patients with AKC when compared with control subjects. These factors may lead to lower stability and wettability of the lacrimal film.^{2,12} Finally, this study found eyes with AKC to have higher messenger RNA expression of membrane mucins (mucin 1, mucin 2, and mucin

4) but lower messenger RNA expression of goblet cell mucin 5AC.^{1,17}

Other. Patients with AKC and AD have increased susceptibility to cutaneous and ocular colonization and infection with *Staphylococcus aureus* and recurrent, occasionally bilateral, herpes simplex virus.^{1,4,14} Colonization by *Staphylococcus aureus* occurs in 66% to 87% of patients with AD but only 6% of control subjects.^{1,14} This increased susceptibility to colonization and infection is believed to be a result of secretory IgA deficiency in sweat and tears and decreased keratinocyte-derived antimicrobial peptides including human beta defensin and human cathelicidin (LL-37).^{4,5,20-23}

Cataracts, both anterior and posterior subcapsular, are another complication of AD and AKC. In severe AD, cataracts occur approximately 10 years after the onset of disease.^{1,14} Cataracts associated with AKC are predominantly anterior subcapsular, but posterior subcapsular cataracts can develop in response to use of oral steroids or steroid eyedrops.^{1,14} Serum IgE levels may correlate with atopic cataracts, and the 56T allele in the gamma interferon receptor 1 gene promoter may be a genetic risk factor for cataracts in AD.¹

Keratoconus (KCN), a condition characterized by progressive corneal thinning that may require corneal transplantation, may also occur in AKC.^{1,2} Chronic eye rubbing in response to irritated eyes induces and further exacerbates KCN. KCN in patients with AKC has been associated with a positive skin prick test result to environmental allergens. Although KCN associated with AD is not significantly different from KCN in nonatopic individuals, atopic patients have a higher incidence of corneal graft rejection.¹

TREATMENT

Management of AKC requires a multidisciplinary approach.⁵ Regardless of the severity of cutaneous findings, all patients with AD and eye signs and symptoms, including blepharitis, conjunctivitis, keratitis, altered vision, KCN, recurrent herpes simplex virus, cataract formation, or glaucoma require evaluation by an ophthalmologist.^{1,2} Signs and symptoms requiring more urgent referral include moderate to severe eye irritation, increased redness, discharge, and any visual symptoms. Treatment of AKC is aimed at controlling symptoms, decreasing recurrence and exacerbations, and reducing vision loss. Although it is important to control AKC, it is equally important to minimize treatment side effects. Treatment options include topical ophthalmic drops: mast cell stabilizers (cromones), antihistamines, corticosteroids,

and calcineurin inhibitors; topical ointments: corticosteroids (ophthalmic) and calcineurin inhibitors; and systemic medications: antihistamines, corticosteroids, and calcineurin inhibitors.^{1,4,5,14,21}

First-line treatment for AKC is the use of topical mast cell stabilizer ophthalmic drops (cromoglycate and lodoxamide 0.1%), which block histamine release from mast cells.²¹ Treatment with mast cell stabilizers is a conservative measure, and they are used, when possible, as corticosteroid-sparing drugs. They can also be useful for maintenance therapy in chronic disease. Dual-acting agents (olopatadine, ketotifen, azelastine, epinastine, and bepotastine), which have both mast cell-stabilizing effects and H1 receptor-blocking effects, can be prescribed if single-acting agents fail.⁴

Topical antihistamine drops and oral antihistamines can be used in conjunction with mast cell stabilizers or other treatments in the management of AKC. Use of antihistamines is aimed at symptomatic relief of pruritus, which is principally mediated by H1 stimulation.^{4,14} Topical H1 receptor blockers are less sedating and thus preferred to oral antihistamines. Second-generation H1 receptor blockers (levocabastine, azelastine, emedastine, bepotastine, and olopatadine) are more specific for the H1 receptor than first-generation H1 receptor blockers. This property makes them less sedating and thus preferred to first-generation H1 receptor blockers.¹⁴ Treatment with topical cromones and topical or oral antihistamines is safe and usually does not require supervision by an ophthalmologist.²¹

Cromones are better tolerated when inflammation has been reduced by pulsed high-dose topical steroid drops or systemic corticosteroids.²¹ In cases of refractory AKC, prolonged courses of low-dose topical steroid drops may be required.⁴ Although corticosteroids are more effective than cromones and antihistamines in controlling AKC, there are many steroid-related side effects including an increase in intraocular pressure, posterior subcapsular cataract formation, and an increased risk of infection.^{4,14,21,24} An ophthalmologist should be consulted when treating patients with topical steroids to minimize side effects.⁴

The calcineurin inhibitors cyclosporine A and FK506 (tacrolimus) affect many immune mediators responsible for AKC and are another form of steroid-sparing therapy. Calcineurin is activated when antigen-presenting cells interact with T-cell receptors. Activated calcineurin then induces nuclear factor of activated T cell, which up-regulates expression of IL-2. Cyclosporine A and tacrolimus block the effects of calcineurin, decreasing production of IL-2.^{4,24} In addition, calcineurin inhibitors inhibit transcription of

Table I. Signs, symptoms and management of atopic keratoconjunctivitis

Disease/condition	Signs/symptoms	Management (in conjunction with an ophthalmology referral)
Blepharitis	Eyelid swelling, irritation, pruritus, and foreign body sensation; may be associated with <i>Staphylococcus aureus</i> infection; meibomian gland disease may develop	Eyelid hygiene regimen—gentle cleansing of lid margin with warm compresses and eyelid scrubs twice daily; ophthalmic antibiotic ointments (including bacitracin, azithromycin, and erythromycin) based on culture sensitivities to reduce bacterial load; aggressive lubrication with artificial tears and ointment, oral doxycycline 20 mg twice daily for 1-2 mo (for children consider azithromycin 10 mg/kg [maximum 250 mg] once daily 3 days a wk for at least 4 wks)
Conjunctivitis	Bilateral, painful conjunctivae with hyperemia and discharge; limbal Horner-Trantas dots during exacerbation	Artificial tears; topical cromone and antihistamine eye drops; aggressive treatment with topical corticosteroid eye drops or systemic corticosteroids for exacerbations
Keratitis	Painful, punctate or frank corneal erosions and shield-shaped ulcers; neovascularization and corneal scarring can lead to decreased visual acuity and blindness	Requires immediate evaluation by an ophthalmologist
Tear dysfunction	Decreased tear film break-up time; dry, irritated eyes	Liberal use of artificial tears, ophthalmic lubrication ointment, and cyclosporine A 0.05% emulsion twice daily
Recurrent herpes simplex infection (active lesions)	Red, painful eye; may lead to vision loss	Oral acyclovir 400 mg 5 times daily in conjunction with immediate referral to an ophthalmologist for evaluation of the cornea
Keratoconus	Blurred vision	Spectacles or rigid gas permeable contact lenses
Cataract	AKC-associated cataracts are anterior subcapsular cataracts, with rapid progression to complete opacification; steroid-induced cataracts are posterior subcapsular cataracts; vision loss	To be evaluated by an ophthalmologist
Steroid-induced glaucoma	Increased intraocular pressure and signs of worsening glaucoma noted by an ophthalmologist	Decrease or stop steroids when possible, and replace with steroid-sparing therapies, such as cromones and calcineurin inhibitors

AKC, Atopic keratoconjunctivitis.

IL-4 and IL-5, decrease production of IL-8 receptor, and block mast cell degranulation by inhibiting production of IgE receptors on Langerhans cells.^{14,24}

Dermatology Cyclosporine A, a cyclic polypeptide of fungal origin, is commercially available as a 0.05% emulsion (Restasis, Allergan, Irvine, CA).²⁵ Two randomized controlled trials using 0.05% cyclosporine A versus placebo (either vehicle or artificial tears) have shown significant improvement in AKC.^{4,26,27} The first randomized controlled trial in 2004,²⁶ which assigned 22 patients with AKC to cyclosporine (0.05%) emulsion 6 times per day

versus artificial tears, showed significant improvement in median symptom and sign grades.⁴ The second randomized controlled trial in 2006²⁷ followed up 40 patients with AKC or VKC for 3 months using cyclosporine 0.05% emulsion 4 times daily versus placebo. Although this trial showed significant improvement in specific signs such as lid margin thickening, conjunctival hyperemia, and corneal tear film deficiency, there was no difference in mean sign or symptom score at the end of 3 months.^{4,26} To our knowledge, there have not been any randomized controlled trials of

cyclosporine A in higher concentrations of 1% or 2% vs placebo. The main adverse effects noted when cyclosporine was used in higher doses (1% or 2%) were ocular irritation and stinging.^{21,27,28} Topical cyclosporine A has been used as a steroid-sparing treatment for patients with AKC, with significant improvements in clinical scores without producing clinically significant elevation in cyclosporine blood levels.^{4,21,28}

Patients with severe refractory AKC unresponsive to topical and systemic corticosteroids may require treatment with systemic cyclosporine.^{4,5,21} Systemic cyclosporine is started at 5 mg/kg daily to induce remission,^{5,21} and maintained at doses as low as 5 mg/kg every fifth day.⁵ Low-dose systemic cyclosporine has been shown to improve symptoms of AKC and visual acuity.⁴

Tacrolimus, a competitive calcineurin inhibitor and macrolide antibiotic isolated from soil fungus *Streptomyces tsukubaensis*, is available as a 0.03% and 0.1% topical ointment (Protopic, Astellas, Toyama, Japan).^{24,29} Compared with cyclosporine, tacrolimus is more immunosuppressive and a more potent inhibitor of IgE-mediated enzyme release.²⁴ Rikkers et al³⁰ studied the effects of 0.03% tacrolimus ointment for atopic lid disease in 5 patients with AD (patients were instructed to place a thin layer of the ointment on the eyelids and avoid placing the ointment directly onto the ocular surface). They found that topical tacrolimus ointment was effective in treating severe eyelid AD, with secondary benefits of improving AKC. Miyazaki et al³¹ studied the effects of compounded 0.02% tacrolimus ointment applied directly to the ocular surface 1 to 4 times daily for 2 to 22 months in 5 patients with AKC refractory to topical steroids. At the end of the study, only 1 patient required topical steroids, and all 5 patients showed significant improvement in clinical and symptoms scores. The main side effect of topical tacrolimus ointment, a burning sensation in the eyes, disappeared after 2 to 4 weeks of continued use. A study by Attas-Fox et al,²⁴ in which topical tacrolimus 0.03% ointment was applied to the conjunctival sac twice daily, was similarly found to be beneficial in patients with SAC. In the experience of 1 author (S. C. P.), application of tacrolimus 0.03% ointment to the eyelid margins twice a day in 7 patients with AKC was helpful in reducing eyelid margin and conjunctival inflammation. There is no Food and Drug Administration–approved ophthalmic formulation of tacrolimus and its use on the ocular surface is currently off-label.

CONCLUSION

Dermatologists should be aware of the ocular findings associated with AD to decrease complications

and the risk of vision loss. AKC can occur at any point during the course of AD and does not necessarily correspond with the severity of the cutaneous findings. Atopic patients with eye redness, irritation, or blurred vision should be evaluated and monitored by an ophthalmologist (Table D).^{1,4,5} All patients receiving treatment for AKC and blepharitis should be treated in conjunction with an ophthalmologist. Ocular signs necessitating immediate referral include: moderate to severe irritation, increased redness, discharge, and any visual symptoms.

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