



Allergic conjunctivitis in children: current understanding and future perspectives

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Purpose of review

The rising global burden of allergic diseases, particularly in the pediatric population, is of serious concern. Ocular allergy is one of the most common ocular pathologies met in clinical practice. A large proportion of children and adolescents suffer from allergic eye diseases (AEDs), which affect their quality of life. The available treatments and surgical modalities have their limitations and side effects. Therefore, the development of novel and alternate strategies is the need of the hour and requires a timely review of currently available knowledge.

Recent findings

The current review covers the incidence and prevalence of AEDs, factors influencing occurrence and severity of AED (age, sex, socioeconomic status etc.), underlying mechanisms, role of allergy testing and immunotherapy in children, development of diagnostic markers and novel therapies including cells and molecules.

Summary

Understanding the demographics, clinical patterns and risk factors of AED can help formulate appropriate preventive and therapeutic strategies for the effective management of this common cause of ocular morbidity. The future therapeutics for AED seems to rely primarily on cells (mesenchymal stem cells, Tregs, mast cells), cell products, molecules with immunosuppressive potential and immunotherapy.

Keywords

allergic conjunctivitis, allergic eye disease, ocular allergy, vernal keratoconjunctivitis, VKC

INTRODUCTION

The external eye epitomizes an ideal site for immediate hypersensitivity reactions due to the large number of mast cells in the eyelids and bulbar conjunctiva, as well as for the potential local synthesis of IgE [1,2]. Allergic conjunctivitis is a collection of heterogeneous ocular inflammatory conditions modulated by activation of mast cells, affecting the conjunctiva, eyelids and cornea [3]. Allergic conjunctivitis may coexist with other allergic diseases including asthma, rhinitis and atopic dermatitis [4]. The disease affects 1/10th to 1/5th of the population and can have significant adverse impact not only on the ocular health, but also on life and productivity in general [5,6]. The WHO has stated that patients with allergy have a suboptimal quality of life, and this predisposes to an adverse economic impact [7]. The World Allergy Organization (WAO) has raised an alarm over the rising burden of allergic diseases worldwide, particularly in the children and in the developing world [7].

ALLERGIC EYE DISEASES

Types of allergic conjunctivitis

The nomenclature of allergic eye diseases (AEDs) is based either on pathophysiology or on clinical signs and symptoms. Different nomenclature systems [IgE-mediated and non-IgE-mediated hypersensitivities by the European Academy of Allergy and

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KEY POINTS

- Big data analysis of a large cohort of patients with AED has provided us with information on demographics, clinical patterns and seasonal variations in disease presentation.
- Literature on the use of allergy testing and immunotherapy is growing, but more evidence is needed to assess the efficacy of these modalities.
- Systemic therapy using anti-IgE antibodies such as omalizumab or T-cell inhibitors such as cyclosporine and tacrolimus is useful in severe and blinding forms of AED.
- Mesenchymal stem cells, mast cells, Tregs, cell products and pathways of immune regulation are areas of active interest for research related to newer therapeutic modalities.

Clinical Immunology (EAACI) [8] and Nomenclature Review Committee of the WAO [9] have been proposed time to time. Recently, Leonardi *et al.* [10] in their position article proposed a new nomenclature based on hypersensitivity and pathophysiology. Accordingly, ocular surface hypersensitivity disorders can be classified into ocular allergy (herein referred as 'AED' and includes IgE-mediated and non-IgE-mediated ocular allergic disorders) and ocular nonallergic hypersensitivity. The major forms of AED are seasonal/intermittent allergic conjunctivitis (SAC), perennial/persistent allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), giant papillary conjunctivitis (GPC) and contact blepharoconjunctivitis (CBC). Both PAC and SAC are IgE-mediated allergic responses. While SAC is more prevalent during spring to fall seasons because of high allergen (pollen) levels, PAC persists throughout the year. VKC is a persistent and severe form of AED that affects children and young adults [11]. It involves IgE-mediated and T-cell-mediated immune responses, cellular infiltration, activation of eosinophils and nonspecific hyper-reactivity. The term AKC is reserved for a persistent, bilateral inflammatory condition which involves the eyelid skin, conjunctiva and sometimes the cornea. It involves IgE-mediated, Th1-mediated and Th2-mediated mechanisms and can be defined as the ocular manifestation of atopic dermatitis. Unlike the previous varieties GPC is a nonallergic hypersensitivity inflammation of the ocular surface, most frequently observed in eyes with ocular prostheses, contact lenses, postoperative sutures and scleral buckles. CBC is an allergic response to different substances which comes in

contact with the eyelid skin or the conjunctival sac, most commonly certain drug molecules or preservatives that are part of ophthalmic formulations.

Epidemiology and clinical features

Ocular allergy is one of the most common ocular pathologies met in clinical practice. It includes different forms, which are collectively termed as AED. A recent study based on electronic medical records driven big data analytics of 259 969 patients (≤ 21 years of age) who presented for an eye examination to a multitier ophthalmology hospital network in India during 2010–2018, reported an incidence of 46 517/million and prevalence of 101 200/million population [12^{••}]. Overall, VKC accounted for three-fourths of all cases. Among these, the palpebral form was most commonly seen in 43%, the limbal form in 15% and the mixed form in around 20% eyes. Corneal complications such as corneal ectasia/keratoconus, limbal stem cell deficiency and shield ulcer were seen in 1.4, 0.4 and 0.3% eyes, respectively (Fig. 1) [12^{••}].

Natural history: seasonal trends

Das *et al.* reported a seasonal pattern (rather than a uniform presentation throughout the year) in presentation of patients to the clinic. A steady increase in proportion of children and young adults presenting with AED was observed with the onset of spring in February, as compared with the usual trend (8.9 vs. 7.7%). This proportion was the highest in the summer in the month of May (12.6%) and then steeply decreased with the beginning of the monsoon in July (7.5%) [12^{••}].

Natural history: demographic factors and comorbidities

The overall prevalence of AED was 0.29% in <1 year of age, 6.56% in toddlerhood (1–2 years of age), 18.25% in early childhood (3–5 years), 15.82% in middle childhood (6–11 years), 8.06% in early adolescence (12–18 years) and 4.89% in late adolescence (18–21 years). The overall prevalence of AED was almost exactly two times greater in males (13%) as compared with females (6.4%). The study by Das *et al.* identified male sex; early and middle childhood age groups; higher socioeconomic class and history of systemic allergy as the high-risk factors of developing AED (Fig. 2). Visual impairment or blindness was rare and seen in only around 1% of the cases. Serious ocular comorbidities were uncommon: cataract and pseudophakia were noted in 0.8%

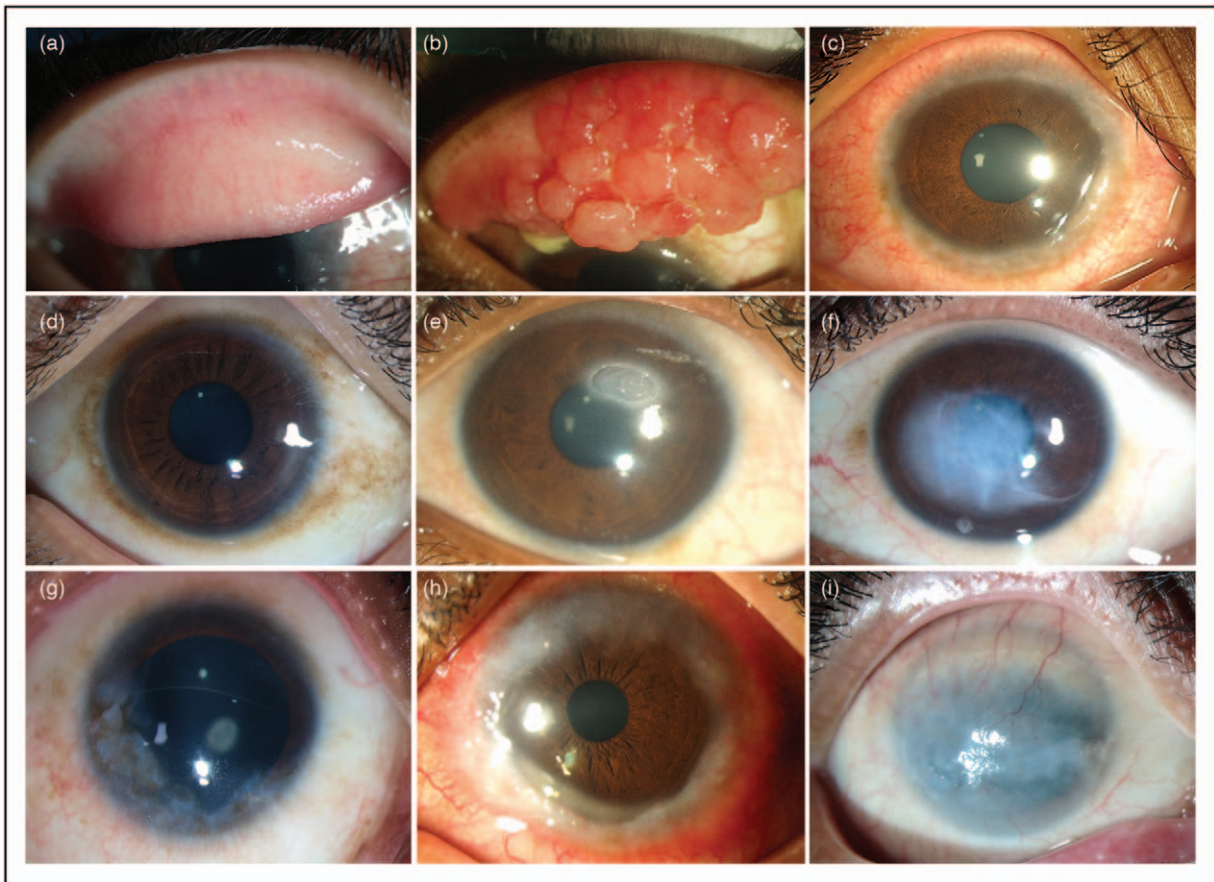


FIGURE 1. Clinical signs of allergic eye disease are tarsal micropapillae (a); macropapillae with discharge (b); limbal thickening (c); perilimbal bulbar conjunctival pigmentation (d); shield ulcer (e); corneal ectasia, scarring and hydrops (f); partial limbal stem cell deficiency with corneal scarring (g); active limbal inflammation with pseudogerontoxon (h); and, total LSCD, limbal stem cell deficiency with corneal pannus formation (i).

eyes, only 0.45% had glaucoma, of which 96% were steroid-induced in cause [12^{***}].

Allergy testing in children with ocular allergies

While numerous in-vitro and in-vivo tests are available, the skin prick test (SPT) is the gold standard due to its reliability in diagnosing IgE-mediated allergic reactions [13]. As per the position article by EAACI on diagnosing ocular allergies, SPT should be performed for pollens, mites, animal dander, *Alternaria* and other allergens based on the patient's history and the common allergens found locally [10]. Serum-specific IgE should be performed if SPT is discordant with clinical history or to quantify specific IgE. In an Egyptian study including 75 patients with allergic conjunctivitis, where both SPT and serum-specific IgE was done for aeroallergens, 42.7% patients had positive SPT. Most prevalent aeroallergens were mites, pollens, grass and hay dust [14]. Non-IgE-mediated allergic reactions

seen in VKC can be tested by patch test using the desired battery. However, this test is not easily available and not routinely performed. Other allergy tests specific to conjunctivitis are conjunctival allergen provocation test (CAPT), total tear IgE level, allergen-specific IgE and conjunctival cytology to demonstrate inflammatory cells – primarily eosinophils. Recently, the Task Force Report of the EAACI Ocular Allergy Interest Group laid down guidelines for use of CAPT in daily practice for ocular surface allergies [15].

Treatment: acute exacerbations and chronic prophylaxis

The clinician dealing with AED in children has a variety of treatment modalities to choose from. Nonpharmacological measures such as avoidance of specific triggers for allergy (if any), cold compresses and counseling the child to avoid eye rubbing are useful across the entire spectrum of disease. Mild episodes of seasonal allergic conjunctivitis may

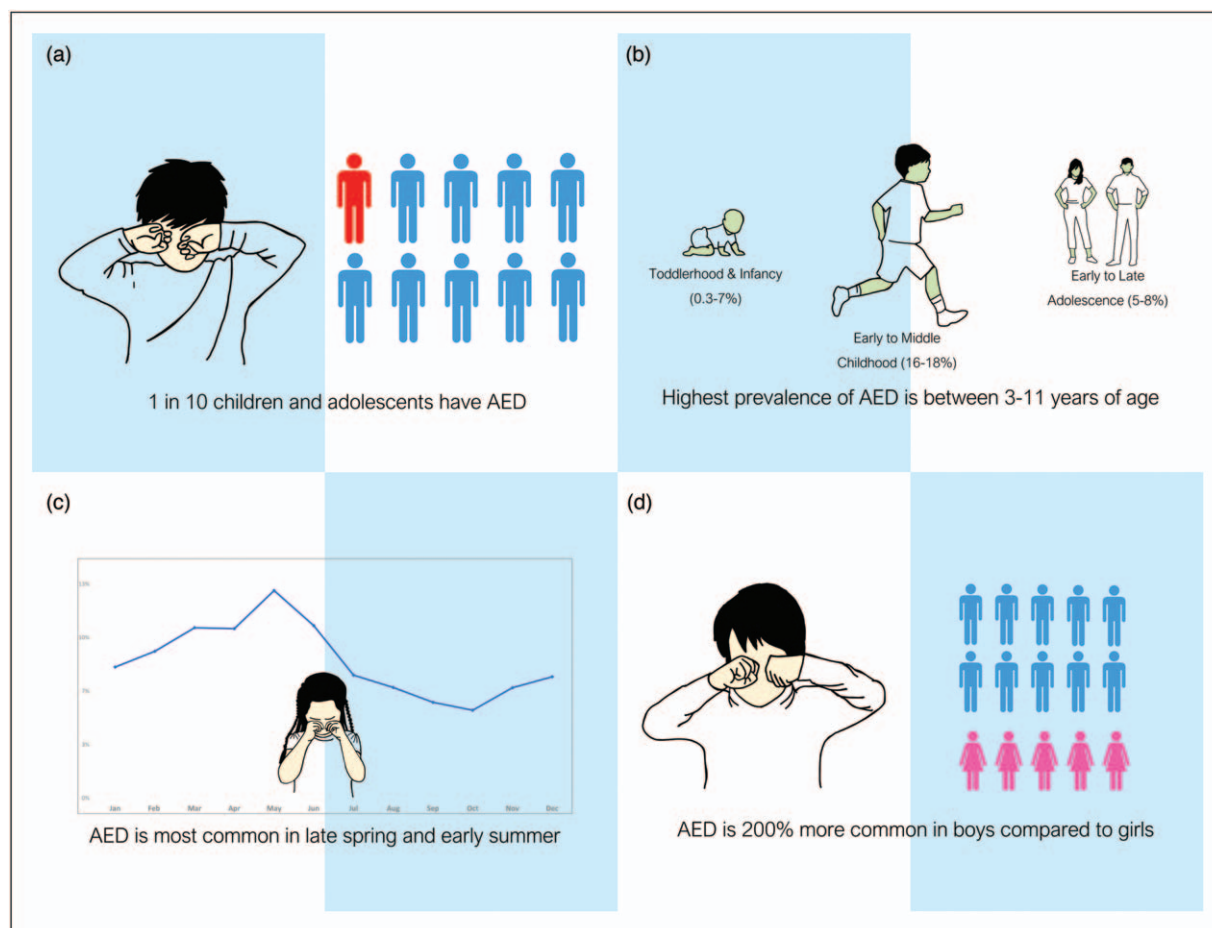


FIGURE 2. Demographics and seasonal trends in allergic eye disease in children and adolescents. A brief caption mentioned below each of the four parts (a-d) is self explanatory. Data from [12²²].

be treated using dual acting agents (antihistaminics + mast cell stabilizers). Many eye drops such as alcaftadine, bepotastine, ketotifen, olopatadine and so on are available, and there is no evidence to support the recommendation of any one particular drug over another [16]. Pure mast cell stabilizers such as cromolyn (cromoglycate), nedocromil and so on have a slower onset of action and are useful as prophylaxis in cases of SAC or PAC. In addition, acute exacerbations may necessitate the use of topical steroids such as loteprednol or fluorometholone for a limited duration.

The clinical presentation of VKC is extremely variable, and we strongly recommend that treatment should be individualized in every case (Fig. 3). The first step is to categorize VKC activity in terms of severity (mild, moderate, severe or blinding) as well as periodicity (intermittent or chronic) [17]. Mild intermittent VKC can be managed using nonpharmacological measures, mast cell stabilizers, dual acting agents and short courses of topical steroids, much like SAC and PAC. Children with more severe and chronic forms of VKC should be actively

screened for complications such as keratoconus, limbal stem cell deficiency, glaucoma and cataract at regular intervals.

In addition to the above measures, children with moderate and severe VKC may require treatment with more potent steroid drops such as prednisolone and dexamethasone in tapering doses or supratarsal injections of depot preparations such as triamcinolone for control of inflammation. Grading of shield ulcers is important, as higher grades tend to require debridement and amniotic membrane application in addition to medical therapy for successful resolution [18]. We find the use of T-cell inhibitor drugs to be of great help as steroid-sparing agents in achieving and maintaining quiescence in moderate-to-severe forms of VKC. Cyclosporine drops have been available for many years, and newer formulations have shown promise in terms of tolerability and efficacy in VKC [19]. In our experience, topical tacrolimus is reasonably well tolerated and has proved to be an extremely useful adjunct for almost all cases of VKC [20²³]. Sublingual immunotherapy has been reported to reduce symptoms in some

MEDICATION	MILD	MODERATE INTERMITTENT	MODERATE CHRONIC	SEVERE	BLINDING
Systemic Immunosuppression	✗	✗	✗	✗	✓
Supra-tarsal Steroid Injections	✗	✗	✗	✓	✓
Potent Topical Steroids	✗	✗	✗	✓	✓
Topical Cyclosporine 1%/ Tacrolimus 0.1%	✗	✗	✗	✓	✓
Allergy Testing & Sublingual Immunotherapy	✗	✗	✓	✓	✓
Topical Cyclosporine 0.5%/ Tacrolimus 0.03%	✗	✗	✓	✗	✗
Low Frequency Topical Lofeprednol	✗	✗	✓	✗	✗
Topical Lofeprednol Pulse	✗	✓	✗	✗	✗
Topical Antihistaminics/ Mast Cell Stabilizers	✓	✓	✓	✓	✓
Avoidance of Eye Rubbing	✓	✓	✓	✓	✓

FIGURE 3. Step-ladder algorithm for the treatment of allergic eye disease in children and adolescents. Data from [17].

specific forms of ocular allergy, and is generally used in cases of allergic rhinoconjunctivitis [21]. More data on the efficacy of this modality would help clarify its role in isolated ocular allergy. Systemic therapeutic options for severe and blinding forms of VKC and AKC include anti-IgE antibodies such as omalizumab and T-cell inhibitors such as cyclosporine or tacrolimus [22–25]. Few reports of the use of these modalities exist at present, but we are favorably impressed by the use of systemic therapy in severe forms of ocular allergy and expect its role to become more clearly defined in the years to come (Fig. 4).

RECENT ADVANCES AND FUTURE PERSPECTIVES

Diagnostic biomarkers of allergic eye disease

Identification of objectively measurable biomarkers that represent the molecular and cellular mechanisms underlying AED is the need of the hour [26]. Novel potential biomarkers can be explored using membrane-based protein arrays to analyze the cytokines present in tears of AED patients. Impression cytology has been found to be useful in assessing ocular surface disorders including AED. The

presence of single eosinophil in the impression cytology samples may indicate allergy and can serve as a marker of AC/AED (Fig. 5).

Microfilm drug delivery

Liu *et al.* studied a microfilm composed of PLCL (D,L-lactide-co-epsilon-caprolactone) with tacrolimus in a murine model of allergic conjunctivitis and compared it with dexamethasone and tacrolimus eye drops. The tacrolimus microfilm delivery system was biocompatible and delivered clinically sufficient doses. This (tacrolimus loaded microfilm) suppressed expression of eosinophils and the CD markers (CD11c, CD4 and IL-4) in immunohistochemical and histopathological staining. This renders a promising clinically applicable alternative for controlling AED [27].

Cell wall components and transient receptor potential antagonists

β -1,3-Glucan, a component of cell wall in a diversity of bacteria, fungi and yeasts, is capable of stimulating IL-10-producing CD4+ T cells and suppressing both the conjunctival infiltration of eosinophils and Th2 response in mouse model of allergic conjunctivitis [28]. Transient receptor potential (TRPV) cation

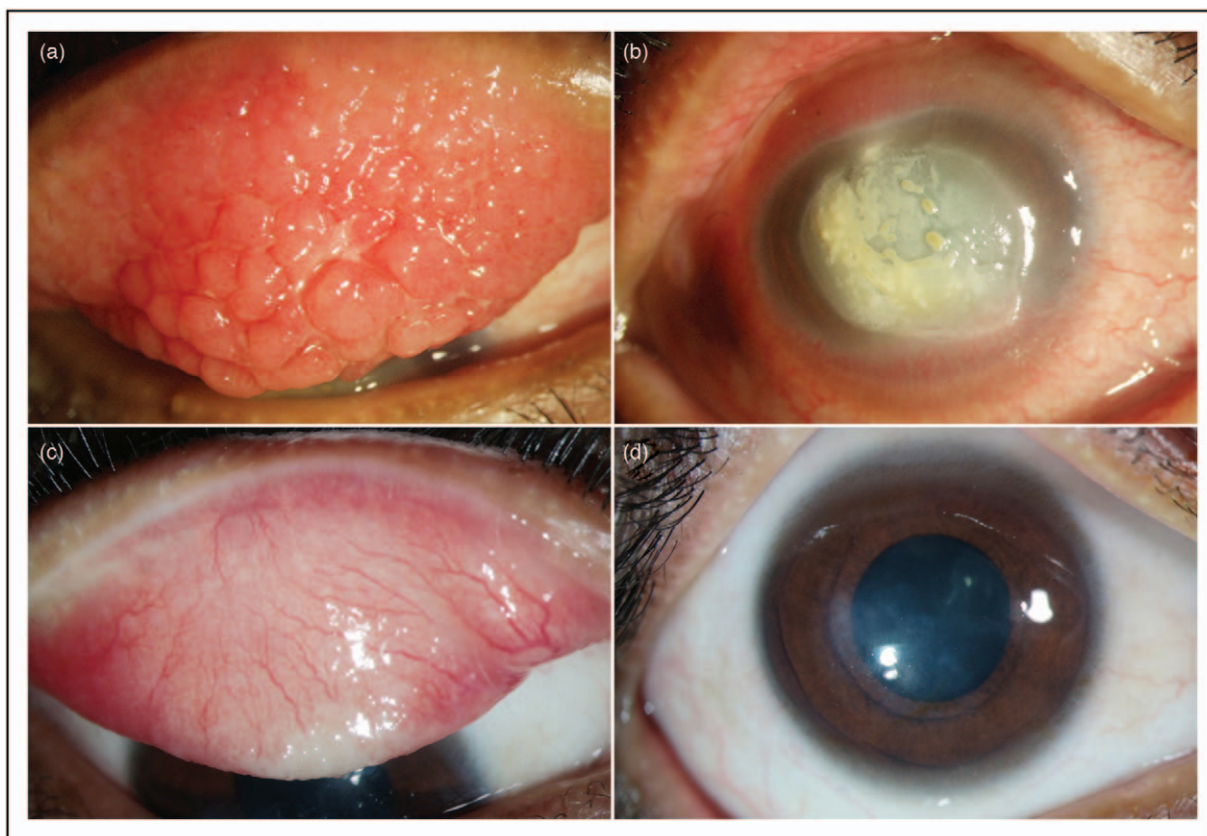


FIGURE 4. Systemic immunosuppression for chronic recalcitrant atopic keratoconjunctivitis. Clinical images of the tarsal conjunctival with macropapillae and discharge (a) and ocular surface showing conjunctival congestion, peripheral corneal vascularization, advanced shield ulcer with dense plaque formation (b) in a 15-year-old child with atopic keratoconjunctivitis. Clinical images of the same child after 2 years of systemic therapy with oral steroids and cyclosporine showing complete resolution of the tarsal macropapillae (c), and a quiet ocular surface with superficial nebular-grade corneal scarring (d).

channel acts as sensor for environmental irritants and is activated by a variety of toxic chemicals present in many plants, food, cosmetics and pollutants. TRPV1 antagonists are reported to suppress the clinical signs of allergy at the conjunctival surface in ovalbumin-sensitized mice that were administered with transient receptor potential cation channel subfamily A member 1/TRPV1 antagonist prior to a topical allergen challenge [29].

Adhesion molecules and transcription factors

The adhesion molecule $\alpha 4 \beta 1$ integrin is expressed in eosinophils interacting with the vascular cell adhesion molecule-1 (VCAM-1) and fibronectin in vascular endothelial cells. It promotes activation and infiltration of eosinophils in allergic conjunctivitis. DS-70, a novel $\alpha 4$ integrin antagonist, prevents the adhesion of $\alpha 4$ integrin-expressing cells antagonizing VCAM-1-mediated degranulation of mast cells and eosinophils and ERK 1/2 phosphorylation, in ovalbumin-sensitized guinea pigs [30]. NF- κ B

(nuclear factor kappa-light-chain-enhancer of activated B cells) is a transcription factor protein that controls cytokine production and cell survival. Topical NF- κ B inhibitors reverse the conjunctival inflammation (induced through benzalkonium chloride) in murine model of allergic conjunctivitis. This highlights the significance of conjunctival tolerance in ocular surface homeostasis and suggests a new pharmacological target for preservative toxicity [31].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have been widely studied for their reparative, regenerative and immunomodulatory properties. These cells have been reported to promote repair and suppress the immune response in damaged and inflamed ocular surface [32–36]. The MSCs have been reported to mitigate allergic immune diseases like asthma [37,38], allergic rhinitis [39] and allergic skin diseases (atopic dermatitis and allergic contact dermatitis) [40–42]. Local instillation of culture medium

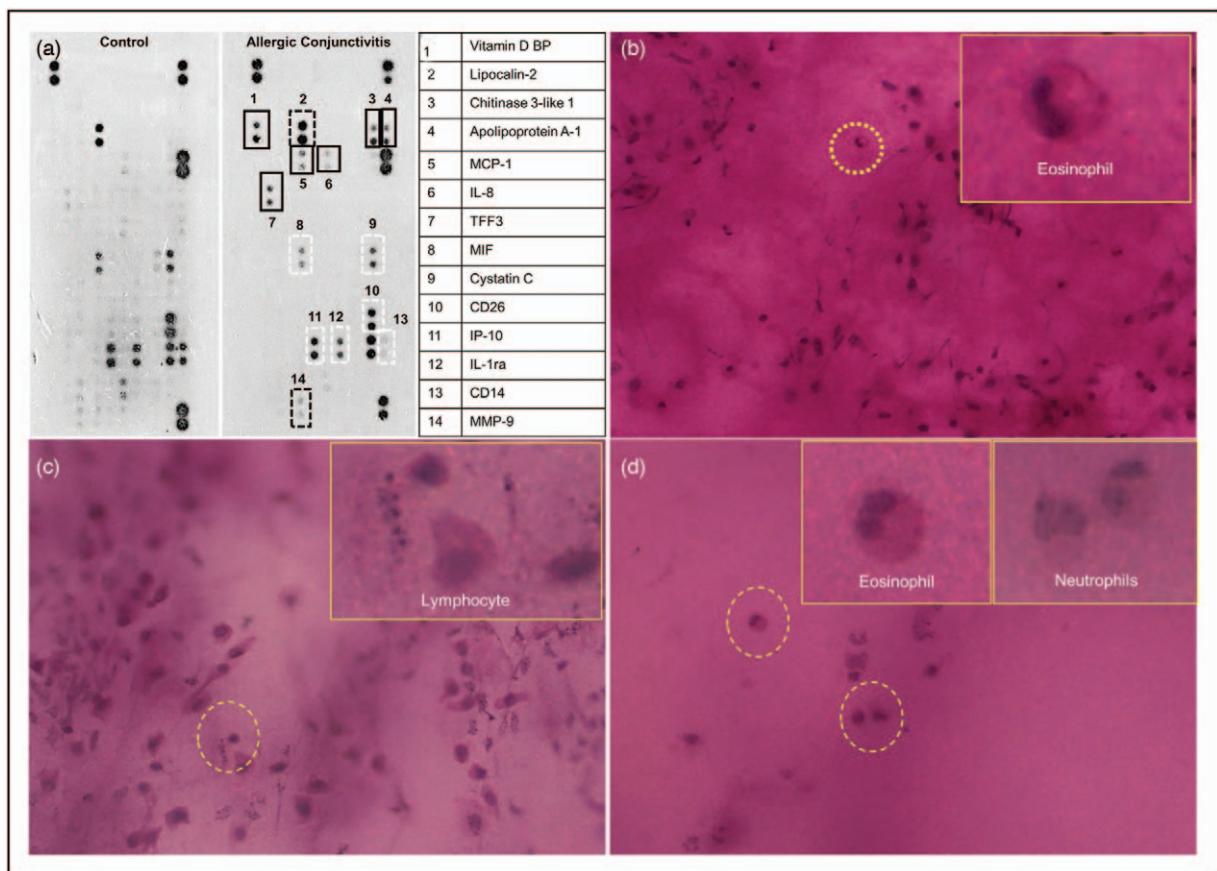


FIGURE 5. Illustrative example of differentially regulated tear cytokines and findings in impression cytology of the ocular surface in allergic conjunctivitis. (a) As compared with healthy controls, tear samples from children with allergic conjunctivitis (b) show differential expression of IL-1ra; IL-8; IP-10, interferon- γ inducible protein-10 (CXCL10); MCP-1, monocyte chemoattractant protein-1; MIF, macrophage migration inhibitory factor; MMP-9, matrix metalloproteinase 9; TFF3, trefoil factor 3; vitamin D BP, vitamin D binding protein. Impression cytology (b–d) of samples collected from children with vernal keratoconjunctivitis show the presence of inflammatory cells (eosinophils, lymphocytes and neutrophils). The dotted yellow circles mark the inflammatory cells which are shown in inset as enlarged images.

derived from TNF- α -stimulated MSCs alleviates clinical symptoms of ragweed pollen-induced allergic conjunctivitis, decreases number of inflammatory cells and secreted molecules (NF- κ B p65, TNF- α and IL-4), suppresses the IgE and histamine secretion, recruitment and activity of mast cells and hyper-permeability of vessels in the conjunctiva [43]. In view of this it is reasonable to speculate that MSCs or MSC-derived conditioned media have the potential to treat AED.

Mast cells

Allergic eye disorders are primarily mediated by the interaction of IgE and mast cells that progress to involve T lymphocytes [44]. Mast cells have historical role in pathogenesis of allergic conjunctivitis [2]. In view of their roles in AED (molecular pathways by which mast cells contribute to immune infiltration

in conjunctiva, mediate activation of other cells and successful targeting of the release of mediators as the main approach in treating AED), mast cells remain the key target in control of allergic inflammation at the ocular surface [2].

Thrombospondin-1

Thrombospondin-1 (TSP-1) is an extracellular matrix protein that is constitutively expressed by ocular surface tissues and regulates various physiological and pathological processes by interacting with a wide range of ligands including growth factors, cell receptors, cytokines and proteases [45]. Topical instillation of TSP-1-derived peptide reduces T-cell activity and clinical progression of AED. This suggests that possible dysregulation of dendritic cell-derived TSP-1 expression may be a factor in severity of AED [46].

Human gut and ocular microbiome

The microbial communities residing in and on the human body (e.g. gastrointestinal tract, airway and skin) along with their genomic elements, metabolites and components together constitute the human microbiome. The microbiome not only plays an important role in early immunological development and immune homeostasis, it also affects the host susceptibility to various immune-mediated diseases including allergy and thus contribute to health and disease [47,48]. Although reports on implications of ocular surface microbiome are not very specific to AED, the ocular surface dysbiosis appears to have a role in AED; and therefore treatments targeting the microbiome may prove to be effective in the management of AED [49].

CONCLUSION

Children and young adults constitute a major proportion of patients affected by AED and some of them have underlying atopic tendencies. This severely affects their quality of life. Recent studies have elaborated on the demographics, clinical patterns and risk factors of AED and helped us identify the at-risk groups like children in early and middle childhood and seasonal patterns which can be targeted for prophylactic therapy. There is some limited role of allergy testing and allergen immunotherapy in ocular allergy [50]. The future therapeutics for treating ocular allergy appears to rely primarily on cells (MSCs, Tregs, mast cells), cell products, molecules with immunosuppressive potential, immunotherapy, or a combination of all of these.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Bonini S. Allergic conjunctivitis: the forgotten disease. *Chem Immunol Allergy* 2006; 91:110–120.
2. Elieh Ali Komi D, Rambasek T, Bielory L. Clinical implications of mast cell involvement in allergic conjunctivitis. *Allergy* 2018; 73:528–539.
3. Abelson MB, Shetty S, Korchak M, et al. Advances in pharmacotherapy for allergic conjunctivitis. *Expert Opin Pharmacother* 2015; 16:1219–1231.
4. Kari O, Saari KM. Diagnostics and new developments in the treatment of ocular allergies. *Curr Allergy Asthma Rep* 2012; 12:232–239.
5. Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. *Curr Opin Allergy Clin Immunol* 2015; 15:482–488.
6. Pitt AD, Smith AF, Lindsell L, et al. Economic and quality-of-life impact of seasonal allergic conjunctivitis in Oxfordshire. *Ophthalmic Epidemiol* 2004; 11:17–33.
7. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J* 2014; 7:12.
8. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001; 56:813–824.
9. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113:832–836.
10. Leonardi A, Bogacka E, Fauquet JL, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy* 2012; 67:1327–1337.
11. Di Zazzo A, Micera A, De Piano M, et al. Adult vernal keratoconjunctivitis: clinical and biochemical profile of a rare disease. *Ocul Surf* 2019; 17:737–742.
12. Das AV, Donthineni PR, Sai Prashanthi G, Basu S. Allergic eye disease in children and adolescents seeking eye care in India: electronic medical records driven big data analytics report II. *Ocul Surf* 2019; 17:683–689.
- The study describes the demographics, clinical features, risk factors and seasonal variations in presentation of allergic eye disease (AED) in a large cohort of patients. The information would be useful for planning prophylaxis treatments as well as for resource allocation.
13. Leonardi A, Doan S, Fauquet JL, et al. Diagnostic tools in ocular allergy. *Allergy* 2017; 72:1485–1498.
14. Abo-Ali FH, Farres MN, Shahin RY, et al. Skin prick test reactivity to aero-allergens among Egyptian patients with isolated allergic conjunctival disease. *Egypt J Immunol* 2015; 22:41–47.
15. Fauquet JL, Jedrzejczak-Czechowicz M, Rondon C, et al. Conjunctival allergen provocation test: guidelines for daily practice. *Allergy* 2017; 72:43–54.
16. Mantelli F, Santos MS, Petitti T, et al. Systematic review and meta-analysis of randomised clinical trials on topical treatments for vernal keratoconjunctivitis. *Br J Ophthalmol* 2007; 91:1656–1661.
17. Gokhale NS. Systematic approach to managing vernal keratoconjunctivitis in clinical practice: severity grading system and a treatment algorithm. *Indian J Ophthalmol* 2016; 64:145–148.
18. Reddy JC, Basu S, Saboo US, et al. Management, clinical outcomes, and complications of shield ulcers in vernal keratoconjunctivitis. *Am J Ophthalmol* 2013; 55:550–559.
19. Bremond-Gignac D, Doan S, Amrane M, et al. Twelve-month results of cyclosporine A cationic emulsion in a randomized study in patients with pediatric vernal keratoconjunctivitis. *Am J Ophthalmol* 2020; 212:116–126.
20. Erdinest N, Ben-Eli H, Solomon A. Topical tacrolimus for allergic eye diseases. *Curr Opin Allergy Clin Immunol* 2019; 19:535–543.
- The review summarizes the outcomes of the use of topical tacrolimus for AEDs. This modality is likely to find a prominent role in future treatment algorithms.
21. Yang J, Zhang L, Zhao Z, et al. Sublingual immunotherapy for pediatric allergic conjunctivitis: a meta-analysis of randomized controlled trials. *Int Forum Allergy Rhinol* 2018; 8:1253–1259.
22. Doan S, Amat F, Gabison E, et al. Omalizumab in severe refractory vernal keratoconjunctivitis in children: case series and review of the literature. *Ophthalmol Ther* 2017; 6:195–206.
23. Hoang-Xuan T, Prisant O, Hannouche D, Robin H. Systemic cyclosporine A in severe atopic keratoconjunctivitis. *Ophthalmology* 1997; 104:1300–1305.
24. Gokhale NS, Samant R, Sharma V. Oral cyclosporine therapy for refractory severe vernal keratoconjunctivitis. *Indian J Ophthalmol* 2012; 60:220–223.

25. Borrego-Sanz L, López Abad C, Méndez Fernández R, *et al.* Oral cyclosporine for severe vernal keratoconjunctivitis in children. *J Fr Ophtalmol* 2019; 42:e12–e13.
26. Roy N, Levanon S, Asbell PA. Potential biomarkers for allergic conjunctival diseases. *Eye Contact Lens* 2020; 46(Suppl 2):S109–S121.
27. Liu YC, Ng XW, Teo EPW, *et al.* A biodegradable, sustained-released, tacrolimus microfilm drug delivery system for the management of allergic conjunctivitis in a mouse model. *Invest Ophthalmol Vis Sci* 2018; 59:675–684.
28. Lee HS, Kwon JY, Joo CK. Topical administration of beta-1,3-glucan to modulate allergic conjunctivitis in a murine model. *Invest Ophthalmol Vis Sci* 2016; 57:1352–1360.
29. Kwon JY, Lee HS, Joo CK. TRPV1 antagonist suppresses allergic conjunctivitis in a murine model. *Ocul Immunol Inflamm* 2018; 26:440–448.
30. Dattoli SD, Baiula M, De Marco R, *et al.* DS-70, a novel and potent alpha4 integrin antagonist, is an effective treatment for experimental allergic conjunctivitis in guinea pigs. *Br J Pharmacol* 2018; 175:3891–3910.
- Novel focus on conjunctival surface adhesion molecules to decrease allergic inflammation of the ocular surface.
31. Guzman M, Sabbione F, Gabelloni ML, *et al.* Restoring conjunctival tolerance by topical nuclear factor-kappaB inhibitors reduces preservative facilitated allergic conjunctivitis in mice. *Invest Ophthalmol Vis Sci* 2014; 55:6116–6126.
32. Basu S, Hertsensberg AJ, Funderburgh ML, *et al.* Human limbal biopsy-derived stromal stem cells prevent corneal scarring. *Sci Transl Med* 2014; 6:266ra172.
33. Basu S, Damala M, Singh V. Limbal stromal stem cell therapy for acute and chronic superficial corneal pathologies: early clinical outcomes of the Funderburgh technique. *Invest Ophthalmol Vis Sci* 2017; 58:3371.
34. Mittal SK, Omoto M, Amouzegar A, *et al.* Restoration of corneal transparency by mesenchymal stem cells. *Stem Cell Rep* 2016; 7:583–590.
35. Shukla S, Mittal SK, Foulsham W, *et al.* Therapeutic efficacy of different routes of mesenchymal stem cell administration in corneal injury. *Ocul Surf* 2019; 17:729–736.
36. Shukla S, Shanbhag SS, Tavakkoli F, *et al.* Limbal epithelial and mesenchymal stem cell therapy for corneal regeneration. *Curr Eye Res* 2020; 45:265–277.
37. Nemeth K, Keane-Myers A, Brown JM, *et al.* Bone marrow stromal cells use TGF-beta to suppress allergic responses in a mouse model of ragweed-induced asthma. *Proc Natl Acad Sci U S A* 2010; 107:5652–5657.
38. Kavanagh H, Mahon BP. Allogeneic mesenchymal stem cells prevent allergic airway inflammation by inducing murine regulatory T cells. *Allergy* 2011; 66:523–531.
39. Sun YQ, Deng MX, He J, *et al.* Human pluripotent stem cell-derived mesenchymal stem cells prevent allergic airway inflammation in mice. *Stem Cells* 2012; 30:2692–2699.
40. Na K, Yoo HS, Zhang YX, *et al.* Bone marrow-derived clonal mesenchymal stem cells inhibit ovalbumin-induced atopic dermatitis. *Cell Death Dis* 2014; 5:e1345.
41. Kim HS, Yun JW, Shin TH, *et al.* Human umbilical cord blood mesenchymal stem cell-derived PGE2 and TGF-beta1 alleviate atopic dermatitis by reducing mast cell degranulation. *Stem Cells* 2015; 33:1254–1266.
42. Su WR, Zhang QZ, Shi SH, *et al.* Human gingiva-derived mesenchymal stromal cells attenuate contact hypersensitivity via prostaglandin E2-dependent mechanisms. *Stem Cells* 2011; 29:1849–1860.
43. Su W, Wan Q, Huang J, *et al.* Culture medium from TNF-alpha-stimulated mesenchymal stem cells attenuates allergic conjunctivitis through multiple antiallergic mechanisms. *J Allergy Clin Immunol* 2015; 136:423–432.
44. Mishra GP, Tamboli V, Jwala J, Mitra AK. Recent patents and emerging therapeutics in the treatment of allergic conjunctivitis. *Recent Pat Inflamm Allergy Drug Discov* 2011; 5:26–36.
45. Foulsham W, Dohlman TH, Mittal SK, *et al.* Thrombospondin-1 in ocular surface health and disease. *Ocul Surf* 2019; 17:374–383.
46. Smith RE, Reyes NJ, Khandelwal P, *et al.* Secondary allergic T cell responses are regulated by dendritic cell-derived thrombospondin-1 in the setting of allergic eye disease. *J Leukoc Biol* 2016; 100:371–380.
47. Rooks MG, Garrett WS. Gut microbiota: metabolites and host immunity. *Nat Rev Immunol* 2016; 16:341–352.
48. Huang YJ, Marsland BJ, Bunyavanich S, *et al.* The microbiome in allergic disease: current understanding and future opportunities – 2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. *J Allergy Clin Immunol* 2017; 139:1099–1110.
49. Cavuoto KM, Stradiotto AC, Galor A. Role of the ocular surface microbiome in allergic disease. *Curr Opin Allergy Clin Immunol* 2019; 19:482–487.
50. Bielory L, Delgado L, Katelaris CH, *et al.* ICON: diagnosis and management of allergic conjunctivitis. *Ann Allergy Asthma Immunol* 2020; 124:118–134.