Good morning, Mr. Chairmen, dear colleagues…First of all let me thank for the kind invitation to participate in this symposium – Late breaking news in allergy.

It will be my great pleasure to review with you recent advances in the understanding of ocular allergy pathogenesis, that I think will help you to establish a correct diagnosis and treatment strategy.
As in other allergic diseases it is possible to classify Ocular Allergy in IgE mediated conditions - such as seasonal and perennial allergic conjunctivitis, and most forms of vernal and atopic keratoconjunctivitis…
...and non-IgE mediated forms that include some cases of the last two diseases but also, giant-papillary conjunctivitis and contact blepharoconjunctivitis.
We will start to follow the pathophysiology of ocular allergy through the dynamics of IgE-mediated acute forms - IgE bound to the conjunctival mast cells triggers a rapid cellular degranulation after contact with the allergen, and a prompt release of vasoactive and pro-inflammatory mediators…leading to conjunctival hyperaemia and oedema (chemosis) typical of acute allergic conjunctivitis (*inset*)
…leading to conjunctival hyperaemia and oedema (chemosis) typical of acute allergic conjunctivitis
Mast cells also produce and store pro-inflammatory cytokines (such as TNF-α), and «Th2» cytokines (IL-4, IL-5) which promote the development of the late allergic conjunctival reaction, with a new histamine peak in tears and the recruitment of inflammatory cells such as eosinophils and T cells. And, clinically, a prolonged hyperaemia with vascular dilatation and oedema (*inset*)
…and, clinically, a prolonged hyperaemia with vascular dilatation and oedema (inset)
One growing area of focus in ocular allergy pathogenesis has been the possible contribution of dendritic and structural cells. Dendritic cells are present in the limbic region of corneal epithelium and in the eyelid skin...
The number of dendritic cells increases significantly in chronic inflammation, and they are seen with macrophages in the conjunctival epithelium...

The number of DCs increases significantly in chronic inflammation, and they are seen with monocytes /macrophages in the conjunctival epithelium...
...allowing the capture and processing of allergens, and antigen presentation to T lymphocytes.
The recruitment and activation of T cells to the conjunctiva is specially relevant to persistent inflammation in the chronic forms of ocular allergy (VKC & AKC).
Cytokines produced by Th2 lymphocytes – IL-4, 13 and 5 – will have a coordinated action in the recruitment and local activation of eosinophils, that through their toxic mediators will induce epithelial lesion, local mast cell activation and the further release of vasoactive mediators, such as leukotrienes.
In the chronic forms of ocular allergy (atopic and vernal keratoconjunctivitis), collagen deposition in conjunctiva, with the formation of papillae and tarsal fibrosis, are characteristic and several mediators and cytokines secreted by both mast cells and eosinophils may promote fibroblast proliferation and activation.
Moreover, a bidirectional interaction with fibroblasts and conjunctival epithelial cells may influence the local differentiation of mast cells (through SCF) and, by the production of chemokines (eotaxin, MCP-1, RANTES) and cytokines (GM-CSF, IL-8) the local recruitment, priming and activation of both conjunctival mast cells and eosinophils.
So, in summary, we can also find some of the characteristic dynamics of the allergic inflammation at the external ocular surface: an acute and transient inflammation may be the dominant picture, usually triggered by mast cell-bound IgE and airborne allergens...
A late phase reaction to the allergen or a chronic inflammation, will be dominated by eosinophils and T cells…
On the other hand, chronic and persistent forms of ocular allergy will progress with fibrosis and tissue remodeling, with papillae formation, conjunctival scarring and blepharitis.
Seasonal (SAC) and Perennial (PAC) allergic conjunctivitis

- Are the most frequent forms
- Bilateral itching is the first ocular symptom, with tears and some burning
- Conjunctival hyperaemia and chemosis, with palpebral oedema are typical
- In SAC the most frequent allergens are pollens; in PAC it is house dust mites.

We will follow now the typical clinical presentation of the different forms of ocular allergy. SAC and PAC are the most frequent, with bilateral itching, tearing, conjunctival hyperaemia and chemosis, with palpebral oedema. The most frequent allergens are pollens, in seasonal forms, and house dust mites in PAC.
VKC is a rare and also typically seasonal form, occurring in children and young adults (usually males), and most of them also have asthma, allergic rhinitis or atopic eczema.

Intense itching, photophobia, burning and frequently blurred vision are seen. Typical giant cobblestone-like papillae are seen in the superior tarsal conjunctiva, that frequently associate with corneal involvement with shield ulcers, as you can see in the picture.
The limbal papillae with white apical gelatinous swellings are rich in eosinophils, fibroblasts and necrotized epithelium - [Horner-Trantas nodules](#).

Tarsal papillae are usually predominant in IgE-mediated VKC.

Limbal papillae with white apical gelatinous swellings - [Horner-Trantas nodules](#) - are also typical of VKC. Tarsal papillae are usually predominant in IgE-mediated VKC.
The analyses of T cell clones obtained from peripheral blood and conjunctival biopsies of VKC have shown a predominance of Th2 cells (with prominent IL-13 and IL-5 production), that could also be found in the conjunctiva. Recent data, with tear fluid cytokine measurements, corroborate these findings in VKC.
Atopic Keratoconjunctivitis (AKC)

- Occurs in adults (18-50 years) with systemic manifestations of atopy and increased serum IgE. It carries the highest risk of blindness.
- Usually there is a family history of atopic diseases.
- It is a chronic conjunctivitis (may last for decades), with smaller papillae in the superior tarsus.
- Conjunctival scaring is frequent and the eyelids are usually inflamed and macerated, with crusts – chronic blepharitis.

AKC is another chronic and usually severe form, typically occurring in young and middle aged males, with systemic manifestations of atopy and increased serum IgE. Among ocular allergic conditions it carries the highest risk of blindness. It is a chronic conjunctivitis, that may last for decades, with frequent conjunctival scaring, chronic blepharitis, potentially complicated with corneal ulcers, as you can see in the slide.
T cell clones obtained from peripheral blood and conjunctival biopsies of AKC have shown a predominance of Th2 cells (with prominent IL-13 and IL-5 production) in peripheral blood, but with a mixture of a Th1-cytokine pattern and IL-10 at the local level.
Giant Papillary conjunctivitis (GPC)

- It occurs due to allergy/intolerance to contact lenses, their cleaning products or preservatives, corneal sutures or ocular prosthesis.
- There is a papillary reaction on the upper eyelid, with or without keratopathy.
- The patient complains of itching and discomfort after insertion of the contact lens.

GPC is considered an iatrogenic form of ocular allergy, occurring in the context of allergy/intolerance to contact lenses, their cleaning products, corneal sutures etc...

Usually there is a papillary reaction on the upper eyelid, with or without keratopathy. The patient complains of itching and discomfort and this condition is usually more prevalent in atopic patients.
Contact blepharoconjunctivitis is frequently an acute form of ocular allergy, due to delayed type hypersensitivity to drugs (topical anaesthetics, antibiotics...), preservatives (benzalkonium chloride, thimerosal...) or cosmetics. The palpebral erythema and oedema dominates, with conjunctival follicles and, frequently, punctiform keratopathy.
So, in summary, the clinical and immunopathological features of the different forms of ocular allergy are very useful for its differential diagnosis and to establish an appropriate management.

With an acute presentation we usually see seasonal and perennial allergic conjunctivitis or contact blepharoconjunctivitis, with opposing involvement of IgE versus Th1-mediated hypersensitivity, and of the tarsal conjunctiva versus the eyelids. Minimal or exceptional corneal involvement is found.
This contrasts with chronic forms of ocular allergy, that are less common, but with frequent corneal involvement (that can be sight-threatening), papillary reaction of the tarsal conjunctiva and conjunctival follicles or nodules. A Th2 and eosinophilic inflammation dominates in VKC (usually a disease of male children) and a mixed pattern, also with Th1 involvement, is found in AKC, that typically associates with atopic eczema or respiratory allergy in an adult male. Finally, GPC is the iatrogenic chronic form, with mechanical factors and local involvement of inflammatory mediators and T cells, with no particular Th1 or Th2 bias.
I will finish my presentation with a diagnosis flow chart proposal…A recurrent red eye is usually first seen by family doctors or pediatricians, that through the characteristic signs and symptoms, personal and family history of allergy, and some laboratory data can establish a presumptive diagnosis of allergic conjunctivitis or keratoconjunctivitis…
Patients with recurrent and chronic forms will benefit from an ophthalmology and allergology evaluation, with a detailed history, slit lamp examination and skin prick tests.

In selected cases other techniques, such as conjunctival cytology, tear fluid analysis and conjunctival provocation may be useful for the final assessment of treatment strategies.