Epidemiology and Pathomechanisms of Ocular Allergy

Michael S. Blaiss, MD
Clinical Professor of Pediatrics and Medicine
Division of Clinical Immunology and Allergy
University of Tennessee Health Science Center
Memphis, Tennessee
Conflicts of Interest

- **Speaker’s Bureau:** AstraZeneca, Sanofi-Aventis, Merck, GSK, Alcon, Teva, Sunovium, Nycomed, Alcon, ISTA

- **Consultant:** AstraZeneca, Sanofi-Aventis, Merck, Alcon, Teva, Sunovium, Proctor & Gamble, Nycomed, Vectura, ISTA, Lupin
Learning Objectives

- Understand the epidemiology of ocular allergy and its burden on the patient
- Be familiar with the cellular, mediator and cytokine mechanisms of both acute and chronic allergic eye disease
Historical Definitions of Hay Fever, or Pollenosis

- “nasal congestion, rhinorrhea, sneezing, mouth breathing, profuse lacrimation, photophobia, conjunctival irritation, edema of the lids, and occasionally chemosis”


- “red eyes, obstructed nose, paroxysmal sneezing and nasal discharge or a watery secretion”

  ---Rackemann, *Clinical Allergy*; p 249: 1931

Early definitions of allergic rhinitis included ocular symptoms as important components of the total symptom complex.
Epidemiology and Natural History of Allergic Conjunctivitis

- Males predominate under age 15 and females predominate thereafter
- There are no differences in incidence between races
- AC improves with age, just as rhinitis does
- Almost all AC patients have a FH of atopy
- 88% of AC pts have AR, 17% have asthma; 11% have atopic derm

Bonini et al, Chap 1, Allergic Diseases of the Eye, Saunders 2000
Kosrirukvongs, Asian Pac Jour of Allergy and Immunol 19:237-244, 2001
Hallmark Signs and Symptoms of Allergic Conjunctivitis

- Diagnosis is usually made by history and clinical examination, particularly in patients with a personal or family history of systemic allergic disease
- Ocular itching
- Tearing and watery eyes
- Hyperemia/redness
- Photophobia
- Chemosis/conjunctival swelling
- Burning/stinging
- Eyelid edema/puffiness

Epidemiology and Natural History of Allergic Conjunctivitis

- Vanna used the ISAAC questionnaire in Brazil: 13% of 6/7 yr old and 13/14 yr old children had ocular allergy symptoms

- Hesselman: Sweden: 19% of 12/13 yr old children had eye symptoms and positive skin tests; 54% of them had taken meds for eyes in the past year

Epidemiology and Natural History of Allergic Conjunctivitis

• Wuthrich study in PCP offices: of 509 patients with ‘hay fever’, 85% had conjunctivitis symptoms. The eye symptoms predominated in 22% of patients, nasal symptoms in 25% and both in 53%

• Eye symptoms were mild in 25%, moderate in 53% and severe in 22%

• Conclusions: eye symptoms are at least as severe as nasal symptoms in patients with hay fever. Eye symptoms are present in almost all HF patients and they are clinical relevant in about 70% of HF patients

Wuthrich et al, Schweiz Med Wochenschr 1998;128: 139-143
Prevalence of allergic rhinitis, allergic conjunctivitis and atopic dermatitis in children with recurrent wheeze

- 260 children with recurrent wheeze for the presence of allergic rhinitis, allergic conjunctivitis and atopic dermatitis by a questionnaire based survey.

- 35% with recurrent wheezing had allergic rhinitis, 15% had allergic conjunctivitis and 19% had atopic dermatitis.

- Nasal and eye allergies were often not recognized.

Allergic conjunctivitis in children with asthma, rhinitis and eczema in a secondary outpatient clinic

- The objective of this study was to assess the cumulative prevalence of allergic conjunctivitis in children with rhinitis, asthma and eczema in a secondary pediatric outpatient clinic in Germany.

- Children aged 5-15 yr referred during the period of 2002-2004 in whom allergic conjunctivitis, asthma, allergic rhinitis or eczema was diagnosed were included in a retrospective survey.

Results

• 458 children with a mean age of 9.4 yr were studied

• AC found in
  • 133 (42%) with rhinitis
  • 78 (24%) with asthma
  • 45 (30%) with eczema

• In children with allergic conjunctivitis
  • 133 (97%) had allergic rhinitis
  • 77 (56%) asthma
  • 45 (33%) eczema

• Allergic conjunctivitis need to be included as an important co-morbidity in future guidelines on asthma, rhinitis and eczema management
Epidemiology of Allergic Rhinitis in Allergy Consultations in Spain: Alergológica-2005

A Navarro¹, C Colás², E Antón³, J Conde⁴, I Dávila⁵, MT Dordal⁶, B Fernández-Parra⁷, MD Ibáñez⁸, M. Luch-Bernal⁹, V Matheu¹⁰, J Montoro¹¹, C Rondón¹², MC Sánchez¹³, A Valero¹⁴,¹⁵ (Rinoconjunctivitis Committee of the SEALC).

Methods

- An observational, descriptive, cross-sectional study was performed in 2005 on a sample of allergic patients treated by 340 allergy specialists in both private and public consultations in the Spanish health system.

- Clinical, epidemiologic, diagnostic, therapeutic and social and healthcare data were collected from 4991 allergic patients treated for the first time in the practices of the researchers involved in the study.
Results

• A diagnosis of AR was made in 2771 of the 4991 patients seen (55.5%)
  • 65% had rhinoconjunctivitis
  • 35% rhinitis

• There were slightly more females (55%) than males (45%) in the rhinoconjunctivitis subsample

• The prevalence of rhinoconjunctivitis was greater in those patients living in damp dwellings (60% vs. 54% in dry dwellings $P < .05$) and in those with air-conditioning (58% vs. 53.6% of patients living in dwellings with no air-conditioning, $P < .01$)
Allergic conjunctivitis: a national cross-sectional study of clinical characteristics and quality of life

Jorge Palmares, Luis Delgado, Manuela Cidade, Maria J. Quadrao, Helena P. Filipe, on behalf of The Season Study Group

1 Ophthalmology Department, Hospital S. João, Porto
2 Immunology Department, Faculty of Medicine, Universidade do Porto, Porto
3 Ophthalmology Department, Hospital de Almada, Almada
4 Ophthalmology Department, Hospitais da Universidade de Coimbra, Coimbra
5 Ophthalmology Department, Instituto Gama Pinto, Lisboa - Portugal
Methods

- To characterize clinical and demographic aspects of allergic conjunctivitis in Portugal, using a structured questionnaire.
- As a secondary outcome, patient’s initial therapeutic and health care options, self-perception of health, and work/school absenteeism were also evaluated.
- A cross-sectional study, in 16 ophthalmology departments of central or regional hospitals, in patients diagnosed with allergic conjunctivitis during the spring of 2006.
Results

- A total of 220 patients were enrolled (mean age of 31.4 ± 18.5 years)
- A quarter of these patients had >5 episodes of ocular allergy in the past year
- 59.3% all year-round episodes
- Most presented associated comorbidities (allergic rhinitis 45.9%, asthma 15.5%)
Results (cont.)

- They had significant impairment of their overall quality of life during an acute episode (45.6% ≥ 6 in a 10-point severity scale).

- Only 19.4% had an appointment with an ophthalmologist as a first action and most (56.1%) started with self-treatment measures.

- Only 37.2% had a previous allergy diagnostic evaluation.
Vernal Keratoconjunctivitis

**Epidemiology**
- Seasonal incidence - vernal-spring/fall
- Occurs primarily in warm climates (Mediterranean, Middle East, Africa)
- 80% are less than 14 years of age
- Boys > girls by 2:1
- Lasts 4-10 years
- 50% have other atopic conditions

**Signs**
- Giant cobblestone-like papillae of upper tarsal conjunctiva
- Highest level of eosinophils in conjunctiva
- Strands of mucus
- 4%-6% can have permanent visual changes
Atopic Keratoconjunctivitis

- Associated with atopic dermatitis
- Occurrence - 2nd to 5th decade of life
- Lid involvement, papillae on lower tarsal conjunctiva
- High Staph colonization of eyelid margins
- More severe disease with corneal complications
  - may be sight threatening
    - vascularization of the cornea
  - secondary infections
Giant Papillary Conjunctivitis (GPC)

- Irritation, mucus discharge, hyperemia
- Enlarged papillae in superior tarsal conjunctiva
- Deposits on soft contact lenses
- Ocular prosthesis, exposed suture, scleral buckle
- Pannus formation
- Type I (tear level IGE increased) and Type IV reaction
<table>
<thead>
<tr>
<th></th>
<th>SAC</th>
<th>PAC</th>
<th>AKC</th>
<th>VKC</th>
<th>GPC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>20–40</td>
<td>20–40</td>
<td>Less than 5 or 20–50</td>
<td>Less than 10</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>M = F</td>
<td>M = F</td>
<td>M more than F</td>
<td>M more than F</td>
<td>M = F</td>
</tr>
<tr>
<td><strong>Season</strong></td>
<td>Spring, fall</td>
<td>Perennial</td>
<td>Any</td>
<td>Spring, fall or perennial</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Red eye</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Itchy eye</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Photophobia</strong></td>
<td>Frequent</td>
<td>Frequent</td>
<td>Constant</td>
<td>Intense</td>
<td>Constant</td>
</tr>
<tr>
<td><strong>Secretion</strong></td>
<td>Watery</td>
<td>Watery</td>
<td>Variable</td>
<td>Mucous</td>
<td>Filamentary</td>
</tr>
<tr>
<td><strong>Eyelid involvement</strong></td>
<td>Oedema</td>
<td>Oedema</td>
<td>Dermatitis</td>
<td>Oedema</td>
<td>Oedema</td>
</tr>
<tr>
<td><strong>Corneal involvement</strong></td>
<td>No</td>
<td>No</td>
<td>Late severe</td>
<td>Limbal, SPK, shield ulcer (10%)</td>
<td>Uncommon (SPK)</td>
</tr>
<tr>
<td><strong>Papillae</strong></td>
<td>Small</td>
<td>Small</td>
<td>Frequent</td>
<td>Giant</td>
<td>Giant</td>
</tr>
<tr>
<td><strong>Serum IgE</strong></td>
<td>78%</td>
<td>78%</td>
<td>Constant</td>
<td>Variable</td>
<td>Constant</td>
</tr>
<tr>
<td><strong>Eosinophils in scraping</strong></td>
<td>25%</td>
<td>43%</td>
<td>Typical</td>
<td>Typical</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Conjunctival goblet cells</strong></td>
<td>Increased</td>
<td>Increased</td>
<td>Reduced</td>
<td>Increased</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Prick / RAST</strong></td>
<td>+</td>
<td>+</td>
<td>+ (aspecific)</td>
<td>+ (55%)</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Association with other allergic diseases</strong></td>
<td>Rhinitis</td>
<td>Rhinitis</td>
<td>Dermatitis Asthma Rhinitis</td>
<td>Variable</td>
<td>Rhinitis</td>
</tr>
<tr>
<td><strong>Personal/family history of atopic diseases</strong></td>
<td>Frequent</td>
<td>Frequent</td>
<td>Constant (95%)</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Response to topical antiallergic drugs</strong></td>
<td>Typical</td>
<td>Typical</td>
<td>Low</td>
<td>Low</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Response to topical corticosteroids</strong></td>
<td>Constant</td>
<td>Constant</td>
<td>Constant</td>
<td>Constant</td>
<td>Constant</td>
</tr>
</tbody>
</table>

SPK, superficial punctate keratitis.
Clinical Relevance of Eosinophils

Eosinophil Cell Count in Allergic Eye Diseases

- Atopic Keratoconjunctivitis (AKC)
- Vernal Keratoconjunctivitis (VKC)
- Giant Papillary Conjunctivitis (GPC)
- Seasonal Allergic Conjunctivitis (SAC)*

VKC, AKC, GPC

- All three are IgE mediated though each probably has cell mediated mechanism which can lead to the corneal damage
- Keratoconus from rubbing can be seen in VKC and AKC
- VKC has Horner-Trantas dots-white spots on the limbus which are collections of degenerated epithelial cells and eosinophils
Trantas Dots
The Allergic Response

1. Allergen is taken up, processed, and bound to the surface of an Antigen Presenting Cell (APC).

2. Antigen-presenting cell activates Th2 lymphocyte which in turn activates naive B cells to proliferate and differentiate.

3. Plasma Cells (B Cell) secrete allergen-specific IgE which bind to sensitized Mast Cells (MC).

4. Allergen binds to IgE and the Mast Cell.
Ocular Allergies and the Mast Cell

- Primary cell involved in the allergic response in the body
- 50 million mast cells in the human conjunctiva

Isolated conjunctival mast cell showing pre-formed granules
Mast cells

- Mast cells particularly abundant in the conjunctival stroma especially at the limbus
- The number of the mast cells in the conjunctiva has been calculated to be $5000/mm^3$
- Conjunctival biopsies from symptomatic allergic patients have shown an increase in subepithelial mast cells with evidence of mast cells degranulation
- Two different types of mast cells have shown in conjunctiva, differentiated by their content of tryptase alone (mucosal mast cell or MCT) or both tryptase and chymase (connective tissue type mast cell or MCTC)
Figure 6  To show the concentration of epithelial and subepithelial mast cells in the different types of allergic eye disease in both tarsal and bulbar conjunctiva. (From Baddiley et al. By kind permission of the publisher of the Journal of Allergy and Clinical Immunology.)

Figure 7  CD4+ T cell numbers in substantia propria in allergic conjunctivitis. (From Mato et al., Anderson et al., and MacLeod et al.)
**Early Phase**

**Degranulated Mast Cell**

**Antigen**

**Other Mediators:**
- Prostaglandins
- Tryptase
- Heparin

**Nerve Stimulation = ITCHING**
3-5 min

**Histamine**

**Endothelial Gaping + fluid leakage = SWELLING**

**Vasodilation = REDNESS**
5-10 min

**Blood Vessel**
Late Phase

Degranulated Mast Cell

Mast Cell Chemotactic Factors

Increase ICAM, VCAM expression on cells and blood vessels

Cytokines

PAF

TNF-α

IL-5

IL-1

IL-4

EPO

MBP

ECP

EOS

NEU

BAS

Recruitment of Eosinophils, Neutrophils, & Basophils

BLOOD VESSEL

Conjunctiva
Tear and conjunctival changes during the allergen-induced early- and late-phase responses

Annette S. Bacon, FRCS,a* Poonam Ahluwalia, PhD,b Anne-Marie Irani, MD,c Lawrence B. Schwartz, MD, PhD,c Stephen T. Holgate, MD, DSc,d Martin K. Church, PhD, DSc,b and James I. McGill, DPhil, FRCSa

Southampton, United Kingdom, and Richmond, Va
FIG 2. The generation of histamine, tryptase, and ECP into atopic subjects’ tears after conjunctival allergen challenge. Tears were collected by cellulose sponges placed in the inferior fornix for periods of 1 minute at the times stated above. Two controls were used: vehicle instillation into the contralateral eye of the subjects receiving allergen challenge and allergen challenge of nonatopic subjects. Each result is the mean ± SEM for group sizes, as defined in the “Results” section. Asterisks indicate significant (P < .05) differences from baseline results in the same subjects.
FIG 3. The expression of the adhesion proteins E-selectin, ICAM-1, and VCAM-1 in bulbar (B) and tarsal (D) biopsy specimens taken from atopic subjects 6 hours after conjunctival allergen challenge. Control biopsy specimens from bulbar (A) and tarsal (C) conjunctiva were from patients with SAC taken out of season. Results are the length of blood vessel endothelium staining with mAbs to adhesion proteins expressed as a percentage of the total blood vessel endothelial length assessed with Ulex lectin. The means of each group of 8 subjects are indicated by horizontal lines. Expression of E-selectin and ICAM-1, but not that of VCAM-1, was significantly greater in both bulbar (E-selectin, P < .01; ICAM-1, P < .01) and tarsal biopsy specimens (E-selectin, P < .001; ICAM-1, P < .01) from allergen-challenged eyes compared with control eyes.
FIG 4. Individual cellular levels in the substantia propria of bulbar conjunctival biopsy specimens 6 hours after allergen challenge in 9 atopc and 22 normal subjects. The means of the counts are expressed as the number of cells per square millimeter. White columns, Control eyes; black columns, challenged eyes (**P < .001, *P < .05 to .003). Antibodies used were AA1 tryptase®; neutrophil elastase; ECP (EG2); pan-T cell (CD3); T-cell subset (CD4); T-cell subset (CD8); and macrophages (CD68; all Dakopatts). MC, Mast cells; N, neutrophils; M, macrophages; E, eosinophils; B, basophils.
In Summary

- Ocular allergies especially SAC and PAC are common throughout the world.
- They add to the poor quality of life in patients with allergic rhinitis.
- These conditions are primarily Type I IgE mediated with both an early and late phase reaction.
- VKC, AKC, GPC probably also have Type IV cell mediated response in their pathogenesis.