Allergic Conjunctivitis in Asia

Dr Bernard Thong
Department of Rheumatology, Allergy & Immunology
Tan Tock Seng Hospital
Singapore
18 Oct 2016
Classification

• Ocular allergies affect 6–30% of the general population

• Allergic conjunctivitis (AC) is associated with rhinitis in 30–70%

• Majority have few episodes of mild conjunctivitis annually

• 30% may have frequent episodes with intense and persistent symptoms (especially seasonal)
# Classification

<table>
<thead>
<tr>
<th>SAC</th>
<th>PAC</th>
<th>VKC</th>
<th>AKC</th>
<th>GPC</th>
<th>CBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>Intermittent</td>
<td>Persistent ± intermittent exacerbations</td>
<td>Chronic</td>
<td>Persistent</td>
<td>Chronic ± intermittent exacerbations</td>
</tr>
<tr>
<td>Allergic Mechanism</td>
<td>IgE-mediated</td>
<td>IgE- and non-IgE-mediated</td>
<td>IgE- and non-IgE-mediated</td>
<td>Nonallergic</td>
<td>Non-IgE-mediated</td>
</tr>
<tr>
<td>Background</td>
<td>Atopic</td>
<td>Childhood ± atopic</td>
<td>Adult atopic</td>
<td>Atopic or nonatopic</td>
<td>Nonatopic</td>
</tr>
<tr>
<td>Eyelids</td>
<td>Edema</td>
<td>Edema</td>
<td>Eczema + meibomitis</td>
<td>Erythema, eczema</td>
<td>Erythema, eczema</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>Follicles and/or papillae</td>
<td>Giant papillae</td>
<td>Papillae ± fibrosis</td>
<td>Giant papillae</td>
<td>±Hyperemia</td>
</tr>
<tr>
<td>Limbus</td>
<td>–</td>
<td>±Thickened</td>
<td>±Thickened</td>
<td>Hyperemia</td>
<td>–</td>
</tr>
<tr>
<td>Cornea</td>
<td>–</td>
<td>SPK</td>
<td>SPK</td>
<td>Rare</td>
<td>–</td>
</tr>
</tbody>
</table>

SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis; GPC, giant papillary conjunctivitis; CBC, contact blepharoconjunctivitis; SPK, superficial punctate keratitis.
Clinical features of the major ocular allergy syndromes: (A) mild conjunctival redness and lid edema in perennial allergic conjunctivitis; (B) tarsal form of vernal keratoconjunctivitis (VKC) with giant papillae; (C) Trantas dots in limbal VKC; (D) limbal form of VKC; (E) central corneal ulcer in VKC; (F) corneal plaque in VKC; (G) skin lesion in atopic keratoconjunctivitis; (H) tarsal papilla in contact lens associated giant papillary conjunctivitis; (I) skin lesion in contact blepharoconjunctivitis.
Epidemiology in Asia

- Few community-based prevalence studies on AC alone
- Hospital-based studies biased towards more severe forms (VKC, AKC)
- Classification of AC with allergic rhinitis (rhinoconjunctivitis) (AR/C)
- Lack of use of validated survey instruments on AC
  - Itchy, watery, red eyes
  - Relation to pollen/animal exposure
  - Doctor diagnosis
- VKC
  - Japan, Thailand, India
  - Onset < 10 yo, most outgrow at puberty
- AKC
  - History of atopic dermatitis, up to 40%
  - Adults 20s-30s

Katelaris CH. Asia Pac Allergy 2011; 1:108-14
Allergies in Asia Pacific Study

Methods
- Across 9 countries, 33,378 households screened
- Nasal allergies, QoL, current treatments
- Telephone and in-person interviews

Results
- 192 children (4-17 yo) and 1,043 adults (18 yo)
- 9% diagnosed with AR, 2/3 seasonal
- Nasal congestion most common and bothersome symptom
- 50% reported that AR impacted their QoL, impairments in school/work performance/productivity
- 2/3 took medication for their AR
- < 25% used intranasal corticosteroid: inadequate efficacy and bothersome side effects

### Ocular Symptoms (ISAAC, AIAP)

<table>
<thead>
<tr>
<th></th>
<th>ISAAC Phase 3 ▲ Current nose &amp; eye symptoms+</th>
<th>ISAAC Phase 3 ▲ Current rhino-conjunctivitis+</th>
<th>AIAP 2009* Red, itchy eyes †</th>
<th>AIAP 2009* Watery eyes †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>20</td>
<td>19</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>China</td>
<td>7</td>
<td>7</td>
<td>32</td>
<td>52</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>24</td>
<td>23</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Korea</td>
<td>12</td>
<td>12</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Malaysia</td>
<td>18</td>
<td>16</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Philippines</td>
<td>11</td>
<td>11</td>
<td>43</td>
<td>62</td>
</tr>
<tr>
<td>Singapore</td>
<td>17</td>
<td>17</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>Taiwan</td>
<td>17</td>
<td>17</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Vietnam</td>
<td>24</td>
<td>24</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Overall</td>
<td>14 X</td>
<td>14 X</td>
<td>31</td>
<td>41</td>
</tr>
</tbody>
</table>

ISAAC: International Study of Asthma and Allergies in Childhood, AIAP: Allergies in Asia Pacific. All figures are percentages. X: total includes countries not included in AIAP survey – India, Sri Lanka, New Zealand. ▲: Adapted from Ait-Khaled et al. [10]. See text for questions. +: in 13-14 year olds. *See Ref 12: response to question: “during the worst month period last year did you have red, itchy eyes or watery eyes”. Answers include those who had symptoms from a few days to every day per week. †Adult populations >18 years.
Natural Allergens and Pollutants

• Urbanization, industrialization and climate change → rapidly occurring changes to both the indoor and outdoor environment → significant implications for prevalence and management of allergic disease, including conjunctivitis

• Rising temperatures, precipitation and more extreme weather
  - Longer/earlier pollen seasons - consequence of ↑CO₂ and temperature
  - ↑sporulation and antigen production of *Alternaria alternata*
  - Potential ↑house dust mite burden

• Outdoor air pollution is a major risk factor for rhino-conjunctivitis; key contributors are fuel combustion and dust storms because of changes in land-use and development

Pollutants

• Relevant air pollutants exacerbating rhino-conjunctivitis include:
  - tobacco smoke
  - pollutants derived from fuel combustion
  - Asian dust – dust storms originating from central/north Asia
  - phthalates - plasticizers for plastic products (e.g. toys, food containers, paints) aerosolize and settle in dust especially in children

• Air pollutants may be allergenic, irritant or a combination of both

• Common pollutants: nitrogen dioxide, carbon monoxide, ozone, sulphur dioxide, particulate matter
Pollutants

- Particulate matter
  - From combustion of coal or fossil fuels associated with power generation or motor vehicle fuels
  - Agricultural burning practices
  - Emissions from domestic solid fuel heaters and woodstoves
  - Classified based on particle size: fine (PM2.5) if 0.1-2.5 mm

- PM2.5 levels were predictive of the number of Tokyo outpatient attendances for AC during non-pollen season \(^1\)

Pollutants - Asian Dust Storms

- Affects much of East Asia during spring
- Dust blown from the deserts of Mongolia, China and Kazakhstan is carried eastwards to Korea, Japan, Russia and even the United States
- Increase in rhinitis visits in Taipei following Asian dust storm

HRQoL from AC in Asia

• Symptoms of AR/C impair the HRQoL of patients by adversely impacting sleep, daily activities, physical and mental status and social functioning

• Measured with SF-36, RQLQ, mini-RQLQ, PRQLQ

• Similar to that demonstrated in much larger numbers of studies of AR/C patients in Europe and the United States

• 'Overall' control of the disease should encompass
  - nasal and ocular symptoms
  - HRQoL
  - comorbid conditions
  - cognition

HRQoL from AC in Asia

- Japanese allergic conjunctival disease (ACD) QoL questionnaire: JACQLQ
- Specific quality of life (QOL) questionnaire
- 521 ACD: 127 healthy volunteers
- Developed by modifying the Japanese rhino-conjunctivitis QoL questionnaire (JRQLQ)
- The items were grouped into four subscales after factor analysis
  - Daily activity
  - Psychological well-being
  - Eye symptoms
  - Nasal symptoms
- Good item-internal consistency (Cronbach's alpha: 0.846-0.934)
- QoL scores were correlated with eye itching, eye irritation and tearing.

## Conjunctival allergen provocation test: guidelines for daily practice

J.-L. Fauquert, M. Jedrzejczak-Czechowicz, C. Rondon, V. Calder, D. Silva, B. K. Kvenshagen, I. Callebaut, P. Allegri, N. Santos, S. Doan, D. Perez Formigo, F. Chiambaretta, L. Delgado & A. Leonardi, on behalf of the Interest Group on Ocular Allergy (IGOA) from the European Academy of Allergy and Clinical Immunology

### Evaluation of Indication

<table>
<thead>
<tr>
<th>Evaluation of Indication</th>
<th>Potency</th>
<th>Level of evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen-triggering factors in ocular allergy</td>
<td>SAC</td>
<td>+</td>
<td>2++/2+</td>
</tr>
<tr>
<td></td>
<td>PAC</td>
<td>+++</td>
<td>2++/2+</td>
</tr>
<tr>
<td></td>
<td>VKC, AKC (selected cases)</td>
<td>++</td>
<td>2</td>
</tr>
<tr>
<td>Doubtful cases</td>
<td>Discrepancy between ocular medical history and allergen sensitizations</td>
<td>++</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Polysensitized patients</td>
<td>+</td>
<td>2–</td>
</tr>
<tr>
<td></td>
<td>Evaluation of anti-allergic properties of topical drugs</td>
<td>+</td>
<td>1+</td>
</tr>
<tr>
<td>Surrogate of mucosal sensitivity to/tolerance of an allergen</td>
<td>Occupational allergy (e.g. latex)</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up of allergy immunotherapy</td>
<td>+</td>
<td>1++</td>
</tr>
<tr>
<td></td>
<td>Food allergy</td>
<td>±</td>
<td>3</td>
</tr>
</tbody>
</table>

SAC, seasonal allergic conjunctivitis; PAC, perennial allergic conjunctivitis; VKC, vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis.
**CAPT**

Instill 20μL (1 drop) in the inferior-external quadrant of the bulbar conjunctiva of:
- Control solution in one eye (control eye)
- Dilution of allergen extract in the other eye

**Evaluate and score for signs and symptoms**

<table>
<thead>
<tr>
<th>Itching(I)</th>
<th>0=none</th>
<th>1-mild</th>
<th>2-moderate</th>
<th>3-severe</th>
<th>4-incapacitating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness(R)</td>
<td>0=none</td>
<td>1-mild</td>
<td>2-moderate</td>
<td>3-severe</td>
<td></td>
</tr>
<tr>
<td>Tearing(T)</td>
<td>0=none</td>
<td>1-mild</td>
<td>2-moderate</td>
<td>3-severe</td>
<td></td>
</tr>
<tr>
<td>Chemosis(C)</td>
<td>0=none</td>
<td>1-mild</td>
<td>2-moderate</td>
<td>3-severe</td>
<td></td>
</tr>
</tbody>
</table>

If Lid Swelling (S) 0=none 1-mild 2-moderate 3-severe

**Repeat with a higher allergen concentration**

- **Positive**
  - HR >2 or TOSS >5
  - **NEGATIVE**

- **NEGATIVE WITH HIGHEST ALLERGEN CONCENTRATION**
  - Monitor for LPR during the next 24h
  - **POSITIVE CAPT**
  - **NEGATIVE CAPT**
  - **Treat**
    - Administer topical antihistamine and/or topical corticosteroids
    - If systemic symptoms administer systemic antihistamines
  - **Keep 2 hours in observation**
  - Discharge only after symptoms had stopped

CPT: conjunctival provocation test; EPR: early-phase reaction; LPR: late-phase reaction

# Management

## Management strategies of allergic conjunctivitis

<table>
<thead>
<tr>
<th>First line</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allergen identification and avoidance</td>
<td>• Consider preservative-free topical therapy</td>
</tr>
<tr>
<td>• Avoid eye rubbing and contact lens wear during symptomatic periods</td>
<td>• Allergen subcutaneous immunotherapy or sublingual immunotherapy</td>
</tr>
<tr>
<td>• Treatment of tear film dysfunction</td>
<td>• Multidisciplinary comanagement with ophthalmology and allergy specialists</td>
</tr>
<tr>
<td>• Use of cool compresses</td>
<td>• Short course of topical ophthalmic ester-based corticosteroid therapy</td>
</tr>
<tr>
<td>• Topical dual-acting antihistamine/mast cell stabilizer agents</td>
<td>• Short course of oral corticosteroid</td>
</tr>
<tr>
<td>• Oral non-sedating anti-H1 antihistamines</td>
<td></td>
</tr>
<tr>
<td>• Treatment of coexistent allergic rhinitis with a nasal corticosteroid</td>
<td></td>
</tr>
</tbody>
</table>

## Third line

- Topical immunomodulator
- Omalizumab if concurrent asthma or urticaria indication
Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface


Topical Calcineurin Inhibitors

- **Ciclosporin CsA (Restasis®)**
  - 0.05% - 0.1% variable efficacy in VKC and AKC
  - 1.00 % and 1.25% for severe forms
  - Case series, systematic review \(^1,2,3\)
  - Side effects - mild and transient burning (2%)

- **Tacrolimus (Protopic®)**
  - 100-fold more potent that CsA
  - Topical 0.005% for steroid resistant refractory VKC
  - 0.03\(^\circ\) and 0.1\(^\circ\) ointment effective over 4-48 weeks
  - * 0.1\(^\circ\) ophthalmic suspension (Senju Pharmaceutical Co., Osaka, Japan) effective by 4 weeks

Topical Ciclosporin

- **Hong Kong**
  - Childhood AC, VKC, AKC (n=14, mean age 10.8 ± 3.2 years)
  - Topical CsA 0.05% Restasis®
  - ↓ symptom, sign, and itch severity scores compared with baseline (p ≤ 0.001)
  - 78.6% of subjects tapered off steroid eye drops
- **Turkey**
  - Placebo-controlled, randomized prospective study, VKC (n=62), 4 weeks
  - Mean post-treatment scores ↓ in CsA vs placebo group (p < 0.001)
  - No adverse effects
- **Japan**
  - Prospective observational post-marketing study from Jan 2006 (n=594, VKC or AKC)
  - 0.1% aqueous ophthalmic CsA
  - ↓ scores for symptoms and signs from month 1-6
  - 30% of steroid users discontinued topical steroids
  - ADRs (12%)
    - Eye irritation (4.4%)
    - Corneal infections (5 AKC): bacterial ulcer (2), herpetic keratitis (3) [all concomitantly using topical steroids]

Topical Tacrolimus

- FK506 (Tacrolimus) 0.01%–1% eye drops inhibit T cell and eosinophil infiltration in the late responses in ocular allergy models in rats and guinea pigs.¹

- Topical FK506 ↓ allergic inflammation in conjunctiva.²
  - ↓ eosinophil and lymphocyte infiltration into subconjunctival tissue in the Balb/c mice of the experimental allergic conjunctivitis model (IP OVA sensitized)

- Tear periostin as potential biomarker of response to topical Tacrolimus?³

- 0.1% Tacrolimus eye drops for refractory allergic ocular diseases.⁴
  - Prospective observational study, refractory allergic conjunctivitis (n=1,436)
  - Poor response to: anti-allergic drugs ± topical steroids ± topical cyclosporine
  - Signs and symptoms ↓ in 1 month, 50% off topical steroids

Allergen Immunotherapy (AIT)

• Improvement in ocular symptoms and signs with
  - Subcutaneous immunotherapy (SCIT) (more for polysensitized)
  - Sublingual immunotherapy (SLIT)
• Duration of effect persists for up to 5 years after termination of SCIT
• Visual analog scale, ocular symptom scores showed a 2-3x improvement
• Conjunctival surface challenge required 10-100x more allergen to provoke a response
• Combined symptom and medication score recommended as the primary outcome measure

Allergen Immunotherapy (AIT)

• Improved total (nasal + ocular) symptom/medication score 27-28% in adults and children
  1. Short ragweed-induced AR/C (randomized, double-blind multinational trial, North America and Europe, adults, n=784)
     • Ragwitek® SLIT tablet - 18-65 years old
  2. Grass pollen AR/C (US adults with grass pollen-induced AR/C, preseasonal and co-seasonal treatment with 300IR 5-grass pollen sublingual tablet, n=473)
     • Oralair® SLIT tablet - 10-65 years old

• Prolonged effect of 5-grass SLIT up to 2 years after treatment cessation

• House dust mite (HDM)-induced AR/C
  1. ↓ nasal and ocular symptoms and exceeded WAO-established clinical efficacy criteria (≥20% improvement vs placebo) by 8 weeks

Conclusion

• *AC* comprises a spectrum of conditions across different age-groups

• Much work done in Japan (basic science, epidemiology, drug development) and Thailand (epidemiology, clinical)

• Topical calcineurin inhibitors effective for severe, chronic *AC*

• Definitive/adjunctive role on AIT in refractory cases or mild seasonal/perennial cases

• Potential for studies on HDM-AIT in Asia AR/C