Diagnostic Tools in Ocular Allergy

Components:

Luis Delgado	Portugal	ldelgado@med.up.pt
JeanLuc Fauquert	France	jlfauquert@chu-clermontferrand.fr
Serge Doan	France	serge.doan@noos.fr
Carmen Rondon	Spain	carmenrs61@gmail.com
Farid Marmouz	France	marmouz.farid@wanadoo.fr
Peter Hellings	Belgium	Peter.hellings@uzleuven.be
Monica Jedrzejczak-	Poland	mjedrzejczak@csk.umed.lodz.pl
Pia Allegri	Italy	pallegri@asl4.liguria.it
Banu Bozkurt	Turkey	drbanubozkurt@yahoo.com
Virginia Calder	UK	v.calder@ucl.ac.uk
Andrea Leonardi	Italy	andrea.leonardi@unipd.it

Banu Bozkurt: Selcuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey
Jean Luc: CHU Estaing, Unité d'Allergologie de l'enfant CHU Estaing 63003 Clermont-Ferrand Cedex1, France
Monica: Department of Immunology, Rheumatology, and Allergy, Medical University of Lodz, Poland.
Sergio: Service d'Ophtalmologie, Hôpital Bichat and Fondation A. de Rothschild, Paris, France

Aim:
This EAACI Task Force aims to provide a comprehensive and complete overview of the currently available tools for diagnosis of ocular allergic diseases. The key issues for inclusion are:

- Describe current methods for the diagnosis of OA
- Promote common nomenclature and procedures between different specialists
- Review available questionnaires and create or adapt a new one
- Available sign and symptom grading scales and create or adapt a new one easy to use for all specialists
- Review the literature for potential biomarkers for OA
- Promote a common workup for the diagnosis
- Identify unmet needs in the diagnostic tools
- Stimulate interest, comprehension and further investigations in this area

Abstract
Introduction: Ocular allergy (OA) includes a group of very and less common hypersensitivity disorders of the ocular surface diagnosed and managed by ophthalmologists but also by allergists, pediatricians, rhinologists and other specialists. However, OA is frequently misdiagnosed and not properly managed. The diagnosis of OA is usually based on clinical history and signs and symptoms, with the support of *in vivo* and *in vitro* tests when identification of the specific allergen is required for patient management. To date, no specific test is available for the diagnosis of the whole spectrum of the different forms of OA. The lack of recommendations on diagnosis of OA is considered a medical need not only for allergists but also for ophthalmologists.

Aim: This EAACI Task Force aims to provide a comprehensive and complete overview of the currently available tools for diagnosis of ocular allergic diseases to promote a common nomenclature and procedures to be used by different specialists.

Results: In the present manuscript we describe current methods for the diagnosis of OA. Questionnaire, sign and symptom grading scales, tests and potential biomarker for OA are reviewed. We also identified several unmet needs in the diagnostic tools to stimulate the interest, comprehension and further investigations in this subject.

Conclusions: Tools and recommendations for the diagnosis of the different ocular allergic diseases are proposed to be used by both allergists and ophthalmologists. We also identified several unmet needs in the diagnostic tools to be further improved by specific clinical research in Ocular Allergy.

Key words:
Allergic conjunctivitis and ocular allergy, [and] diagnosis / investigation / workup [and] imaging [and] questionnaire / quality of life / QoL [and] grading or scoring [and] visual function [and] tear sampling [and] biomarkers [and] differential diagnosis [and] psychological impact [and] tear function

Manager of the paper: Andrea and Virginia

Introduction and Current Classification of Ocular Allergy

The term allergic conjunctivitis (AC) refers to a collection of ocular surface disorders that affects the lid and conjunctiva. IgE- and non-IgE-mediated hypersensitivity disorders include seasonal and perennial allergic conjunctivitis (SAC and PAC), vernal and atopic keratoconjunctivitis (VKC and AKC) and contact blepharoconjunctivitis (CBC) (1) (Table 1). These diseases are diagnosed and managed not only by ophthalmologists but also by allergists, pediatricians and rhinologists usually considering clinical history and signs and symptoms, with the support of *in vivo* and *in vitro* tests when identification of the specific allergic sensitization is required for patient management (1). While their clinical characteristics allow a relatively convincing diagnosis, in their initial or chronic stages there can be some confusion as to which form of allergy is present. At times, pseudo-allergic forms, with clinical manifestations similar to allergy but with a non-allergic equivocal pathogenesis, are difficult to distinguish from ocular allergic forms. In fact, several ocular surface diseases, including tear film dysfunction, blepharitis, subacute and chronic infections, toxic and mechanical conjunctivitis may mimic the clinical pictures of ocular allergy. To date, there is no specific clinical and laboratory test suitable for the diagnosis and monitoring of allergic conjunctivitis. Ancillary tests, such as skin prick and the identification of serum specific IgE, can be useful for diagnosis and treatment, however it is well known that the results are often not correlated with the ocular disease.
As in many other diseases, effective prevention, curative treatment and accurate, rapid diagnosis and particularly the lack of recommendations on diagnosis of ocular allergy, represent major unmet needs (2). This EAACI Task Force aims to provide a comprehensive and complete overview of the currently available tools for diagnosis of ocular allergic diseases to make recommendations concerning the diagnosis of ocular allergy (OA) in daily clinical practice.

Methods **to be better explain the biblio search**
A systematic review of the literature was performed in Pubmed and Science Direct databases, using the following key words: Allergic Conjunctivitis or Ocular Allergy [AND] Diagnosis workup, Investigations, Imaging, Questionnaire / QoL, Scoring/ Grading, Instruments / Specific tools, Clinical, Visual function/acuity, Ocular sampling/Tears, Tear Function, Biomarkers, Psychological impact.
Confounding diagnosis of terms ocular allergy (MESH): not allergic hypersentivity such as Stevens Johnson syndrome, graft versus host disease, were eliminated using a filter: NOT *(Stevens OR dacryo* OR retina OR uveitis OR gvh OR optic nerve)*
If number of references reasonable, manual selection and report at the end of this file. If number to large, link is integrated in the table (table 2)

Hand searches of the reference lists of selected studies were performed and relevant studies identified. Experts were contacted to suggest other studies not previously encountered in the database search. Studies were considered if they included human subjects, irrespective of age and race, and addressed diagnostic procedures,

diagnostic utilities, irrespectively of the type of the ocular allergic disease in which they were performed. No time or language limitations were established. Papers were selected according to the information provided on the title and abstract for the covered topics of the review. From the ???? retrieved papers, each topic was reviewed by two independent experts and, finally, ???? papers were included and analyzed. Evidence to support each point was reviewed and a consensus decision was made for each chapter. As the evidence approaching a diagnostic procedure was scarce, some of the recommendations were based on consensus-driven proposals from the task force working group

Patient's clinical history

Rationale

The patient's medical history is the first and a very important step in the diagnosis of the OA, especially in the differential diagnosis of "Red Eye" which is one of the most common ophthalmologic conditions (3). Well-performed anamnesis may provide data to help in resolving the etiology of the red eye.

The medical history should cover types of symptoms (itching, burning, photophobia, type and amount of discharge, visual changes, severity of pain), unilateral or bilateral eye involvement, duration of symptoms, presence of allergies or systemic diseases, previous treatment, family history, environmental and occupational exposures, use of contact lenses and any type of ocular surgery (1).

Signs and symptoms

Ocular itching, evaluated by the patient, is the hallmark subjective symptom of allergic conjunctivitis. It indicates the release of histamine from conjunctival mast cells and the activation of H1 receptors on nerve endings (30). Ocular redness (hyperemia) is the primary sign of allergic conjunctivitis due to a vasodilatation. Photographic scales can be very useful to minimize subjective observer variability of conjunctival hyperemia (see later). Secondary signs and symptoms are tearing (or watery eyes), conjunctival chemosis, and lid swelling all evaluated by the physician.

Itching. It is the hallmark symptom of OA, especially if it is moderate or severe. Mild itching may be also observed in viral conjunctivitis and in dry eye (1). Eyelid itching is referred by blepharitis patients and especially if related to eyelash infestation.

Tearing. ……

Hyperemia. Hyperemia is often present in ocular allergy with a typical diffuse location. In the situation of local hyperemia a differential diagnosis with, subconjunctival hemorrhage and episcleritis should be considered.

Severe symptoms occur particularly in AKC and VKC although they can be sometimes encountered in SAC and PAC.
Pain. Pain is not a typical symptom of the ocular allergy conditions SAC or PAC. However the presence of pain is a sign of corneal involvement as a complication of disease in VKC and AKC.

Visual disturbances. The typical allergic patient may report mild blurring or normal vision. However the visual impairment is a sign of corneal involvement as a complication of VKC and AKC.

Discharge. Frequently present in OA. Both intermittent and perennial forms may have intermittent discharge. If it persists, dry eye or any form of tear film dysfunction should be considered. The type of discharge is crucial: in OA discharge is usually watery or serous. The mucopurulent or purulent discharge evokes infectious conjunctivitis. Bilateral discharge upon awaking is a sign of blepharitis. Sticky mucous discharge and tearing especially if associated to severe photophobia in a child are significant for VKC.

Signs and symptoms outbreak modalities

Unilateral or bilateral involvement. Bilateral involvement is typical for ocular allergy. It is very useful for differentiation diagnosis. However, non-symmetrical forms are possible. In viral conjunctivitis for example the symptoms are often unilateral at onset and become bilateral one or two days later.

Time of onset. First symptoms of SAC and PAC appear mostly in adolescents and young adults (80% of patients are younger than 30 years old), but can also start in older patients (4). VKC usually begins in boys aged 3-12, rarely but possibly before the age of 3. The symptoms often disappear after puberty (5). It is observed more frequently in warm climates. VKC is more frequent in Mediterranean basin, Middle East, Far East, Africa and South America (6). In AKC, eye symptoms may appear years after skin involvement and appear usually at 30-50 years old (7). Overlaps or evolutions from VKC to AKC may occur.

Duration of symptoms/Environmental and occupational exposures. One of the most important points in the clinical history is the duration of symptoms. SAC is caused by exposure to plant pollens and spores. The onset and duration of symptoms are limited to the pollen season in which high atmospheric concentrations of these allergens are reached and they recur every season although their severity may differ. It is self-limiting when the season is over (8). In PAC, symptoms are usually mild but persistent and exacerbate after increased or long-lasting exposure to allergen or unspecific irritating factors. The patient should be asked about symptoms after contact with main allergens like house dust mite, animal dander, latex or molds (9, 10). PAC and AKC may also present with seasonal exacerbations. VKC worsens in the spring and summer but, if severe, the symptoms can be observed all year round.

Other circumstances. Patients being diagnosed for giant papillary conjunctivitis (GPC) should be asked about contact lenses or ocular prostheses as well as previous ocular surgeries. A detailed contact lenses history should be taken (11). In CBC a detailed medical history has to be taken with a special attention to different substances that could be applied into or around the eye (medications, cosmetics etc.). If there is a possible work-related OA it has to be confirmed by worsening of symptoms in the workplace (1, 12). Some nonspecific factors like smoke, pollution or wind can increase symptoms of the OA diseases (10). In addition food or food additives like tartrazine may influence the ocular disease.

Family history/Co-morbidity. Many patients have a history of other allergic diseases or the family has a history of other atopic diseases. Allergic conjunctivitis or conjunctival symptoms are present in 30-71% of patients with allergic rhinitis (10). Allergic conjunctivitis alone has been estimated in 6-30% of the general population and in up to 30% in children alone or in association with allergic rhinitis(13). Up to 40-75% of VKC patients suffer from other allergic diseases like asthma, allergic rhinitis, atopic dermatitis or urticaria (13). AKC is present in up to 40% of atopic dermatitis patients. In the active period the co-morbidity with atopic dermatitis and asthma is around 90% (14).
Finally, apart from eye symptoms it may be necessary to consider the patient's activity limitations, sleep problems, coexisting nose, respiratory and cutaneous problems but also practical and emotional aspects.

Recommendations

- Accurate medical and personal history
- Red eye differential diagnosis
- Always ask for ocular signs and symptoms in other allergic co-morbidities
- Investigate triggers for signs and symptoms
- Refer to ophthalmologist (red eye DD)
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Unmet needs

- Primary care awareness on ocular allergy
- Standardized questionnaire to be used by both ophthalmologists and allergists
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Clinical Ocular Examination

Rationale

Some macroscopic clinical signs can be assessed by non-ophthalmologists (Table 3). Most of them are not specific for allergy and may be present in any type of conjunctivitis: ocular redness, conjunctival and lid edema, mucous discharge,
The clinical diagnosis of ocular allergy thus relies on the combination of a suggestive medical history and signs of conjunctivitis. Some specific signs of VKC or AKC may be

visualized by macroscopic examination, such as superior tarsal conjunctival giant papillae (only visible after lid eversion) and limbal inflammation with Trantas dot. These 2 signs may be considered as severity signs, because leading to the diagnosis of severe forms of OA. Lid eczema is also a very specific marker for ocular allergy. Examination of the ocular surface by ophthalmologists may disclose various other signs such as conjunctival papillar hypertrophy, follicules, or scarring, blepharitis (lid margin inflammation) and meibomian gland dysfunction (MGD), and tear instability. The 3 latter signs are important for the frequent differential diagnosis of evaporative dry eye related to MGD. Corneal involvement is a marker of severity and is present only in VKC and AKC : superficial diffuse punctate epitheliopathy, neovascularization and scars are non specific, whereas shield ulcers and vernal plaques are much more suggestive of severe allergic keratoconjunctivis.

Techniques

- Day light or direct light observation of the face, lids, lid margin, palpebral and bulbar conjunctiva.
- Lid eversion provides access to the superior palpebral conjunctiva. When the patient looks down, pull down the superior lashes then apply a flat stick on the superior half of the lid. Evert the lid by pulling the lashes up.
- More accurate ocular examination requires the use of a slit lamp and a biomicroscope. Corneal and conjunctival epitheliopathy are thereby assessed by using fluorescein and a blue light.

Recommendations

- Always look at the eyelid skin and the lid margin
- If you don’t have a slit lamp, look at the eye using natural light where possible
- Look for severity signs
- Examination by an ophthalmologist may be required in atypical or severe cases

Scoring Ocular Allergy and quality of Life

Rationale and Definitions

For clinical practical purposes, grading systems of conjunctivitis severity have been proposed including questionnaires and signs and symptoms scores. Different scales and criteria have been used, indicating the difficulties encountered to assess either acute or chronic disease manifestations. Main indications for scoring ocular allergy signs and symptoms include the evaluation of the severity of the disease, the assessment of the response to provocation tests (CPT and NPT) (see below) and the evaluation of the efficacy of therapeutic agents. Thus scores can be repeated during the follow-up of ocular allergy.
Health related quality of life (QoL) has been defined as "the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient". OA may significantly impact daily activities and occupations like reading, computer or tablet use, recreation, games, sports, television, movies, electronics.These disturbances generate worries, anxiety and some psychological discomfort for the patient, mostly for children and family. QoL instruments aim to describe these effects. The impact of OA on daily tasks, work, leisure, sleep and mood as perceived by the patient is important to consider, as a marker of severity. To date, no specific quality of life (QoL) questionnaire has been validated for OA, except in VKC. The reason might be the differences in symptoms and impacts on QoL between SAC, PAC, AKC and VKC. In terms of important patient-reported outcomes, the ocular component of allergic rhinitis impacts patient QoL in meaningful ways (15).

Instruments

1. *Grading Signs and Symptoms*

The VAS is a useful alternative semi-quantitative method to express the intensity of symptoms by the patients. The recording is performed on a 100-mm scale without marked intervals by indicating the most severe symptoms on the far right and the absence of symptoms on the far left. The recording is explained to the study participants by a study clinician, but the VAS should be self-administered by the patients. The VAS scale is particularly used in clinical research (31). The severity of subjective symptoms may be ranged from (0) to (10). The slit lamp findings can be scored according to severity from (0) to (3): a grade of (0) is scored for no signs, (1) for "mild", (2) for "moderate" and (3) when "severe" signs or symptoms are present.

Grading questionnaires
In the OSDI questionnaire, the score is based on the duration of symptoms. The score is 0 if the symptom is absent, 1 if present "some of the time", 2 if present "half of the time", 3 if present "most of the time", and 4 if recorded "all the time". In the

QUICK questionnaire (18), the score is defined as : a three-point scale: 1 = never, 2 = sometimes, and 3 = always. The total score obtained as the sum of scores recorded for the different individual symptoms included in the evaluation determines the status of the disease.

Ocular Severity scores

The "Severity Index"-system is based on the subjective assessment of the patient regarding the grade of severity of each particular symptom and its evolution. In this SI-system, the score of (3) is recorded for "severe" manifestations, a score of (2) for "moderate" manifestations, a score of (1) for ''mild'' manifestations and a score of (0) for the situation where no specific symptom is manifested. The status of disease with the SI scoring system is determined by the sum of the recorded scores for the individual symptoms included in the evaluation (Table). In 2012 the EAACI Ocular Allergy Position Paper (1, 32) proposed a severity classification of OA disorders based on ARIA guideline criteria (32)(5,6). The selected items are quoted "yes" or "no" for vision disturbance, impairment of daily activities/ leisure/ sport, impairment of school or work activities, troublesome symptoms. According with the number of items affected the OA is considered "mild" (0 items affected), "moderate" (1 item affected) or "severe" (2-4 items affected).

2. *Scores for therapeutic agents evaluation*

To evaluate the efficacy of new pharmacologic agents on rhinoconjunctivitis, it has been suggested to use either adjusted form of symptoms score (symptom score adjusted for the use of rescue medication), or a combined score consisting typically of a (weighted) sum of symptoms and rescue medication scores (RMSs) (33).

For clinical trials on the efficacy of immunotherapy in allergic rhino conjunctivitis, measurements of both symptoms and the use of rescue medication (34, 35) are needed. The Average Combined Score (ACS) calculated is the average of the rhino conjunctivitis total symptom score (ARTSS) and the average rhino conjunctivitis medication score (ARMS). It should be considered as a primary efficacy variable for allergic rhino conjunctivitis in clinical trials on immunotherapy (33, 34). The ACS (WAO) has a range from 0 to 3, taking into account the stepwise regimen of the three categories of rescue medication used. Thus higher classes of rescue medication used lead to a higher ARMS and so to a higher ACS (WAO) (34). Rhino conjunctivitis allergy-control SCORE (RC-ACS) assesses the severity of nasal and ocular allergy by considering symptoms and use of anti-allergic medications (36). It includes a full list of relevant drugs, without exclusion. Each score can be used separately or in combination. Thus, RC-ACS can be used in daily practice to grade real-life situations.

3. *Quality of life evaluation and questionnaires*

QoL questionnaires

Generic QoL questionnaires assess global health status in a general population. The most frequently used scales are: the Short form 36 and 20 (SF-36 and SF-20), the EuroQoL (EQ-5D), and the Sickness Impact Profile (SIP) (16). The KINDL questionnaire is dedicated to children (17).

QoL in OA

In the absence of specific questionnaires for OA, questionnaires validated for allergic rhino conjunctivitis are used. The Juniper's Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (19) and its shortened version, the mini RQLQ (20), are the most commonly used questionnaires in adult patients. The RQLQ includes 28 items divided in 8 domains. The mini RQLQ has been reduced to 14 items and 5 domains : activity limitations, practical problems, nose symptoms, eye symptoms, other symptoms. Juniper et al have also developed specific questionnaires adolescents and children (21, 22). Ocular allergy is addressed in five symptoms in the RQLQ and 4 in the mini RQLQ : need to rub nose/eyes, itchy eyes, sore eyes, watery eyes, and swollen eyes (not in the RQLQ). Interestingly, the analysis of 4 clinical trials revealed that, among the 28 RQLQ items, the highest scoring items were the need to rub eye/nose and itchy eyes (20). In a large cohort of 1009 rhinitis patients, the presence of ocular symptoms statistically increased the RQLQ score by +0.5 (23).
Among OA, VKC and AKC should probably be considered separately, because the impact on the patients QoL is often intense. Moreover some ocular symptoms related to keratitis, such as photophobia and mucous discharge, are severity symptoms. Sacchetti et al developed a specific QoL questionnaire for VKC patients, the QUICK(18). It contains 16 items, pooled in 2 domains: symptoms and daily activities. In contrast to children with rhinoconjunctivitis (22), daily activities like going to the swimming pool, practicing sports of meeting friends, were show to impact dramatically QoL in children affected by VKC. The QUICK questionnaire showed good correlation with the generic KINDL QoL questionnaire. It has been validated for children aged 5 to 12, and is available in Italian and English (ref).

Eye-related QoLs, OA excluded.
Some questionnaires have been developed for dry eye patients, such as the Ocular Surface Disease Index (OSDI) and the impact of dry eye on everyday life (IDEEL). Even not specifically addressed to ocular allergy, they may be interesting in order to assess the dry eye components in PAC for example.

Impact on economic costs.
Considering the prominence of computer monitors and visual tasks in the modern workplace, the effects of ocular symptoms on productivity are of great concern. SAC patients experienced QoL reductions in general health and specific aspects of vision, but also a significant economic cost to treat their condition when assessed by the Health Economic and Demographic Questionnaire (HEDQ)(24). This aspect must be taken into account for both private and public health care modalities when attempting to ascribe a total cost to a medical condition. Visual function can also be assessed with the Visual Function (VF)-14 or the VFQ25.

Recommendations

- Scoring signs and symptoms is recommended for diagnosis and monitoring
- VAS scoring system, widely used in clinical research, gives the patients' perspective
- Consider an assessment of impact of ocular allergy on QoL, however a specific questionnaire is missing

- The EuroQoL (EQ-5D) gives at least the basic information on general QoL
- In the absence of a specific questionnaire on ocular allergy the miniRQLQ can be used
- The QUICK is the only specific and validated questionnaire for VKC

Unmet needs

- Universal, definitive severity scoring syste
- Correlation among currently available severity scoring systems is still unknown
- Specific QoL questionnaires should be developed to study ocular allergy impact on vision, general and psychological condition in different ages
- The ideal tool could measure disease and symptoms perception and treatment effectiveness by the patient

Tests to diagnose ocular allergy

Rationale and definitions

In the diagnostic process of OA, the allergen may be considered as either the main factor triggering symptoms, closely associated with non-allergenic factors, or unrelated to clinical symptoms. Allergens account for the main inflammatory mechanisms on the ocular surface, by triggering the cascade of IgE mediated allergy. Currently, skin prick tests (SPT) are unanimously considered the gold standard and the first-line approach to detect IgE mediated sensitization, due to its efficiency, safety and relatively low costs (37). The biological assays are considered a second choice, to be used only in special situations. Once sensitization is demonstrated, its relevance for the patient should be investigated. The specific conjunctival provocation (CPT) should be considered, particularly when polysensitization is evidenced or in cases when clinical history is suggestive of ocular allergic reaction but SPT and IgE are negative or inconclusive (1) (Fauquert submitted).

IgE mediated investigation is indicated in the majority of cases of SAC and PAC. The relationship between allergen sensitization and the allergen exposure is easy to assess in many case, particularly of SAC. However allergic investigation may not be necessary in cases where symptoms resolve with symptomatic treatment, or when symptoms occur after an obvious allergen exposure. Conversely, when symptoms persist (PAC) or repeat (SAC) regardless of treatment, allergic investigation is needed. VKC and AKC require IgE mediated investigation and, when medical history point towards contact allergy, non IgE mediated data. Not IgE mediated allergy can also account for some cases of contact blepharoconjunctivitis, and also in some cases of VKC and AKC (1).

Techniques

Skin Tests

The skin prick test (SPT) technique is currently considered the gold standard method for the diagnosis of IgE mediated allergen sensitization. SPT should be performed with airway and some food allergens, and read according to a rigorous methodology following the EAACI recommendations (38). Indications of intradermal tests are limited to selected cases and allergens. Patch-tests aim to explore non IgE mediated allergy (Brasch 2014). Haptens involved may be preservatives or additives of eye drops, cosmetics, or professional allergens. Most of time, the European battery is tested in addition to cosmetics or eye drops used by the patient.

Specific IgE measurements

The method most frequently used to measure serum allergen-specific IgE is an immune-enzymatic assay. In vitro IgE sensitization is assessed over 0.1 IU/mL although low serum levels (< 0.35 IU/mL) of specific IgE are less likely to be clinically relevant. Measurements of specific IgE are less sensitive than SPT (39, 40) and not mandatory when SPT correlate with the clinical history. The presence or absence of specific IgE in the serum does not imply a clinically relevant allergy. Local sensitization is highly suspected in the eye (41). In such cases, microarray measurements of specific IgE in a small quantity of tear could be helpful in the near future (38). Total IgE level is not recommended for allergy diagnosis since its variations significantly correlate with atopic background. Comparing the serum and tear total IgE dosages could be considered as an indirect method for assessing local release of IgE and thus for evidencing local allergy (42).

Conjunctival provocation test (CPT)

CPT, also known as conjunctival allergen challenge (CAC) or ocular challenge test, is used to evaluate the inflammatory effects on the ocular surface after the topical application of an allergen **(1)**. Thus allergen sensitization must be evidenced before performing instillation of allergen, unless the exposure environment is convincing of allergy but no sensitization is assessed (43). Recommendations were published recently on behalf of the EAACI (PP Fauquert submitted and 39). A positive CPT triggers the same symptoms (itching and tearing) and signs (redness, chemosis and lid swelling) as those of a natural exposure to the allergen. Contraindications are limited to uncontrolled allergic and chronic diseases as well as acute impairment of the ocular surface. In daily practice, it requires an informed consent, an ophthalmologic examination to rule out any inflammation of the ocular surface in a clinic able to manage side-effects, and a controlled protocol based on precise positivity criteria. Itching and redness are the main criteria to achieve a positive response when score 2+ (30). The IGOA Task Force on CPT in daily practice recommend to assess the reproducibility of the provocation test, the use of total ocular symptom score (TOSS; range 0 -13), including subjective plus objective criteria, to be considered positive when the cumulative scoring reaches 5 (Table 2) (PP Fauquert Submitted). Monitoring of both early and late allergic response should be considered. Since allergic response to CPT may induce both ocular and nasal symptoms, scoring of nasal symptoms is useful. Conversely a NPT is considered

positive when the cumulative symptoms score of the 4 classical nasal symptoms - Linder Symptom Score Scale (LSSS; range 0-13) - is equal or higher than 5 points (33). However there is a lack of a standardized method for evaluating the combined ocular and nasal symptoms in response to CPT or NPT. Despite the safety of this simple and fast tool to assess ocular or other IgE-mediated allergic diseases, it is clearly underused in daily clinical practice. Nonspecific challenge tests are only used for research purposes (39).

Recommendations

- If results of skin prick test, IgE levels and allergen exposure history are in concordance, the involvement of the allergen can be assumed.
- Otherwise CPT should be considered, particularly if multiple sensitizations are suspected.
- CPT is recommended when medical history suggests an allergen, even if SPT are negative
- In VKC and AKC, allergen-specific triggering is less frequently involved.
- When contact blepharitis or blepharo-conjunctivitis is suspected, patch-tests are required.

Unmet needs

- There is a lack of a standardized method for evaluating the combined ocular and nasal symptoms in response to CPT or NPT.
- Microarray evaluation of specific IgE to allergens are required particularly in tears,

Assessing consequences of OA

Psycho environmental consequences
Rationale and

Visual Function

Rationale

Allergic Conjunctivitis is usually not considered as a sight-threatening disorder. Its clinical presentation ranges from mild forms not (or slightly) influencing VF to severe diseases (VKC and AKC), which affect the ocular structures, visual acuity (VA) and QoL. Complications (corneal impairment, irregular astigmatism and scars, keratoconus, cataract, steroid-induced glaucoma) result in visual impairment (25). Visual disturbances are also caused by symptoms (intense itching, watering, foreign body sensation, mucus discharge, eyelid pseudo-ptosis, ocular pain and photophobia). Few population-based data on VA testing and impairment in OA are available since VA rarely represents a primary or secondary outcome of therapy in clinical trials.

Definition
VA "is a measure of the spatial resolution of the visual processing system" which means the ability to discriminate in the space two separated stimuli in conditions of high contrast to the background, which is determined by a comparison with the normal ability to define certain letters at a given distance, usually 20 feet (6 meters).

Techniques
In normal clinical practice, VA is measured by asking the subject to discriminate letters of known visual angle (Snellen and derived optotypes) or letters of equal recognition difficulty, and use the log of the minimal angle of resolution at a given distance and at high contrast (ETDRS and similar). Measurement of VA follows a psychophysical procedure and can be performed by using an eye chart, by optical instruments, or by computerized tests, with standard conditions, like correct luminance of the eye chart, correct viewing distance, enough time for responding, etc.
Electronic VA testers are more comfortable in infants, pre-verbal children and special populations (for instance, handicapped individuals).
Although the value of vision sometimes is difficult to measure in VKC and AKC during acute phases, visual QoL can be quantified as a surrogate criterion (26).
A study on the best-corrected VA in subjects suffering from VKC shield ulcers showed that, after ulcer re-epithelization, VA improvement depends on the severity of shield ulcers (27).
Adequate time and attention should be given to take a complete and accurate VA examination. All VKC and AKC patients should routinely undergo topographic corneal assessment because of the higher incidence of keratoconus in atopic diseases (28, 29). Association between OA and KC….

Recommendations
- Consider VA assessment as a primary outcome in daily practice
- VKC and AKC subjects should undergo topographic corneal examination to rule out keratoconus

Ocular surface evaluation (Tear film function)

Rational
Chronic conjunctival allergy is a cause of evaporative dry eye. Simple tear film evaluating tests ….

Definition
- Dry eye is classified as hypo-secretory or evaporative.
- Schirmer test quantifies the tear secretion, whereas break-up time (BUT) assesses tear film stability.
- Tear hyper-osmolarity is a marker of dry eye.
- Low tear lipid layer thickness is related to meibomian gland dysfunction (MGD), tear instability and evaporative dry eye.

Techniques

BUT

Invasive BUT (O): Insert a wetted fluorescein strip in the inferior conjunctival fornix, and remove when tears are stained. Use blue cobalt light +/- yellow filter for observation. After a few blinks, ask patient not to blink and measure time between the last complete blink and tear film break (when black striae appear in the precorneal tear film). Repeat measure 3 times. Mean values below 10 seconds reflect tear instability and evaporative dry eye(44).

Non invasive BUT – NIBUT (NO): Some specific devices like some corneal topographs, aberrometers, measure NIBUT.

Schirmer test

Insert a nitrocellulose Schirmer strip into the inferior conjunctival fornix, at the external third of the inferior lid. Measure the length of wetted strip within 5 minutes. A test without anesthesia is recommended as being more reproducible. Values below 5 mm reflect aqueous deficient dry eye(44).

Tear osmolarity can be measured by an osmolarimeter, after tear sampling. The Tearlab® device provides an immediate result after automated collection of a few nanoliters. Values beyond 312 mOsm/L are abnormal.

Tear lipid layer thickness can be measured by interferometers like the Lipiview® (Tearscience) or the DR1® (Kowa).

Recommendations

- Consider that tear film dysfunction can be caused by OA.
- Dry eye and OA can coexist.

Ocular Sampling

Rational and definition

Samples can be easily obtained from the ocular surface making cytological tests and mediator search an attractive tool in OA.

Technique

Different methods for tear collection can be used: capillary tube, filter paper, ophthalmic sponges and eye washes (45).

Aspiration of tears by glass capillary tubes or pipettes can yield volumes of 20–50 µl. However tear collection is tedious, time-consuming, and sometimes uncomfortable for patients and children, and may provoke the production of reflex tears by touching the conjunctiva with the capillary (46, 47). Tears can be recovered from a Schirmer's strip which is routinely used in the ophthalmology clinic as a standard clinical test to assess the tear quantity in patients with dry eye syndrome (see

above). Strips tend to collect some cellular proteins which may come from epithelial conjunctival cells, moreover tear reflex is common due to strong irritation by the strip (48). Various sponges (cellulose sponges, porous polyester rods, polyurethane mini sponges, cellulose acetate filter rods) can be placed in the lower tear meniscus and held for a fixed period of time (49, 50). For the eye wash technique, a fixed volume of saline is instilled into the inferior fornix and the fluid collected by a capillary tube (51). It may be useful where the tear volume is very low, however it is impossible to determine the original tear volume and the dilution of proteins.

Recommendations

- It is preferable to collect samples independently from both eyes since in many cases there is an asymmetrical clinical presentation.
- Capillary tube collection is preferable since cells and mediators may bind to the strips or sponges, and diffusing cytokines out of the device during the extraction procedure can be difficult.

Tear biomarkers

Rational and definition

The tear fluid is an extremely complex biological mixture containing cells, proteins/peptides, electrolytes, lipids, and small molecule metabolites, which can be measured for diagnostic, prognostic and experimental purposes. Tear collection is not painful or traumatic, with only its insurmountable limitation regarding the quantity of sample obtainable. The challenge in the analysis of tear fluid is the high dynamic character of the tear proteome, and the small sample size, therefore the total amount of proteins that can be used for analysis is low when compared with blood. Tear protein analysis was limited to a few analytical techniques dependent on antibody availability. With increasing proteomic applications, tears show great potential as a source of biomarkers in the development of clinical assays for various human diseases. The concentration and distribution of proteins and inflammatory mediators in tears have been extensively used in OA to find either a ‘disease marker’, to understand better the immune mechanisms involved in the ocular surface inflammation, or to identify potential targets for therapeutic interventions.

Techniques

Cytology

A cytological test can be performed using tears, conjunctival scrapings, impression cytology or conjunctival biopsy. For tear cytology, a few microlitres of tears collected from the external canthus with a glass capillary are immediately placed on a slide. Conjunctival scrapings, performed with a spatula or a brush, allow for the collection of a good amount of epithelial and inflammatory cells (if present). Pre-colored slides, or rapid dyes can be used for a response in a short time. Impression cytology refers to the application of cellulose acetate filter to the ocular surface to remove the superficial layers of the ocular surface epithelium (52). Conjunctival biopsy (performed under topical anesthesia) is required when a neoplastic pathology or

autoimmune diseases is suspected. Papanicolaou or haematoxylin and PAS stains are the commonly used stains for routine histological staining of specimens. Samples can be also used for different immunostaining, flow cytometry techniques, RNA or DNA extraction, all depending on the number of cells collected.
In patients with allergic conjunctivitis, the cellular constitution of the tear film is characterized by the presence of neutrophils, eosinophils and lymphocytes (53). A secondary immediate, late and delayed conjunctival responses, induced by the nasal provocation test with allergen (NPT), were associated with different cellular profiles in the tears (54). By flow cytometry, the percentages of T cells, activated B cells, and T-helper/T-suppressor cell ratios were found to be higher in tears of patients with AKC than in controls (55). Using intra-cytoplasmic cytokine expression, an increase in Th2 lymphocytes in tear fluids of patients with VKC has been demonstrated (56).

Tear protein analysis
Total protein concentration decreases significantly if the tear samples are kept at room temperature for 4-8 h and further drops to 70-80% of the original concentration after 16 h (57). Tear samples can be kept up to one week at 4˚C, up to 2 months at -20 ˚C, and up to 4 months at -70˚C with very small loss of protein (58).

- As tears contain various enzymes and hydrolases, proper storage of tear samples is an important issue to prevent sample loss and unreliable results. (move to text)
- The ultimate outcome could be affected by the tear collection method chosen and the consistency of the extraction protocol making it difficult to assess the feasibility of the protocols and to compare the results between different studies (49). (text)

Dozens of mediators, cytokines, chemokines, growth factors, angiogenic modulators, proteases, enzymes and inhibitors have been identified in small tear samples using new methods such as multiplex bead arrays, membrane-bound antibody array and proteomic techniques in addition to the traditional ELISA or RIA (59).
Total and specific IgE have been measured in tears to improve the diagnosis of IgE-mediated allergic conjunctivitis (41). Patients with high total tear IgE have a high probability of allergic sensitization, however measurement of tear allergen-specific IgE antibodies is a more specific diagnostic maker of allergic sensitization (42, 59).
The increased tear concentrations of tryptase and histamine have been considered biomarkers of allergic conjunctival response (see for review(59)).
The measurement of eosinophil cationic protein (ECP) in tears has been considered a valid tool in monitoring ocular allergic diseases, and in the evaluation of topical therapies (60-62). Although several cytokines, chemokines and their receptors have been found over-expressed in allergic ocular inflammations, none of them seems to be ideal to be used as clinical biomarker (59).
Proteomic analysis of tear fluid has proven to be a promising approach to gain more information about the pathogenesis of diseases and lead to new diagnostic possibilities. Increased hemopexin concentration in VKC tears was found to be significantly associated with disease severity (63). Levels of serum albumin, transferrin and hemopexin were found up to 100 times higher in VKC tears than controls and correlated to the severity of disease (64). In addition, hemopexin,

transferrin, mammaglobin B, and secretoglobin 1D were found significantly overexpressed in VKC samples compared with the control samples (64).
Excluding assays for total IgE and MMP-9 specifically designed for tears, no local tests have been standardized for clinical use and probably no single factor or test is considered as a specific disease marker.
More likely, a combination of several of them may be required to indicate a single disease phenotype, activity phase, or therapeutic effect.

Recommendations

- The presence of even one eosinophil in cytology is highly indicative of an allergic pathology, whereas their absence does not exclude an allergic diagnosis
- Tear collection and storage can influence biomarker detection

Unmet need

- One possibility would be to design an assay kit to detect a panel of tear markers, including total IgE, tryptase, eotaxin, ECP, IL-4, IL-5, MMP-9 which have been found consistently increased in ocular allergic diseases and validate it in the different ocular allergic phenotypes.

Imaging and emerging additional tests

Rational

In-vivo imaging technologies including in-vivo confocal microscopy, meibography, tear film interferometry and photography have been widely used in the diagnosis, assessment of clinical severity and follow-up of ocular surface disorders. The application of these technologies to detect the pathological alterations in the conjunctival epithelium, cornea, meibomian glands (MG) and the tear film structure related to OA may help to quantify the extent of inflammation and evaluate the efficacy of allergic agents.

Definition and Techniques

In-vivo Confocal Microscopy (IVCM) is a real-time, in vivo, non-invasive imaging technology, which enables microstructural analysis of cornea in more physiological conditions at a cellular level (65). In contrast to conventional microscopes, which are limited by light scatter from structures outside of the focal plane, IVCM create a point source of light by a pinhole aperture, focused by an objective lens on the tissue. The light reflected by the tissue is then collected by a parallel objective lens, focused onto a separate pinhole aperture, and collected by a detector. Compared to traditional slit lamp imaging, IVCM provides a higher magnification and depth of view, but examine only a limited area. With the more recent introduction of the in-vivo laser scanning confocal microscope (LSCM), it became possible to study the microscopic anatomy of translucent and semi-opaque structures, such as the conjunctiva and meibomian glands (MG) (66, 67).

Clinical Applications in Ocular Allergic Diseases

To identify the morphological changes in cellular and neural structures in cornea and conjunctiva. In VKC, cornea imaging with LSCM showed increased diameter, reflectivity, and presence of nuclear activation of superficial epithelial cells, lower density of keratocytes, increased presence of activated keratocytes, and inflammatory cells in the anterior stroma in close proximity to the subbasal and stromal nerve fibers (68). Infiltration of Langerhans cells and inflammatory cells in epithelium and stroma, and the destruction of Vogt Palisades were found at the limbus (69). Similar findings were described In AKC, where the densities of cornea basal epithelial cells, subbasal long nerve fibers and total nerve branches were found to be lower than normal eyes (70). Polymorphic and dendritic cell densities in the conjunctiva and cornea were found to be significantly higher compared with healthy control subjects which correlated well with the number of inflammatory cell numbers in brush cytology (71, 72).

Cell density of the mucocutaneous junction epithelium, MG acinar unit density and diameter, glandular orifice diameters, meibum secretion reflectivity, and appearance of the glandular interstice and acinar wall, were all found significantly worse in AKC patients compared to obstructive MG dysfunction patients and controls (73).

Clinical Applications in the CAC model

Following CAC, IVCM can be used to track the progress of the acute allergic response and the subsequent ocular late phase inflammation, capturing video images useful to study dynamic events, such as leukocyte-endothelial cell rolling and arrest in human ocular vessels overlying sites of inflammation (74). Increased numbers of white cells within the vasculature adhering to vessel wall or in process of diapedesis were shown after CAC (75). A conjunctival inflammation confocal scale (0-4) (patent pending), to grade the leukocyte presence and adhesion in and around the conjunctival blood vessels has been proposed.

This may become particularly useful to evaluate the efficacy of allergic medications in terms of presence of inflammatory cells in the conjunctiva and cornea as well as in measuring changes in epithelial integrity and papillae pathology. In AKC patients, the addition of topical cyclosporine A (CsA) to topical steroid and anti-allergic treatment showed a significantly lower density of inflammatory cells and remarkable fibrosis in papillae (76). Similarly, after a 3-month treatment, topical CsA reduced the number of conjunctival, limbal and peripheral cornea DCs in VKC patients (77).

Meibography is a non-invasive technique developed to observe the structure of MG in silhouette, by illuminating the eyelids from the skin side, and can detect their morphological changes. There are two techniques: contact and non-contact using either a light probe directly applied onto the eyelid or infrared (IR) filter and IR charge-coupled device video camera (78, 79). The evolution of meibography has recently accelerated with the advent of non-IR technologies including laser confocal meibography and OCT meibography (67, 73, 80-82).(reference 83 might be excluded)

Clinical Applications in Ocular Allergy

MG shortening, distortion and dropout may be observed easily. PAC and contact lens associated allergic conjunctivitis were found to be associated with increased MG duct distortion in half of the patients (83, 84).

Lipid Layer Interferometry measures tear stability by imaging the surface contour of the tear film and analyzes the depth or ‘‘thickness’’ of the lipid layer. Normally, a thick lipid layer spans the tear surface in a continuous manner, whereas a thin lipid layer degenerates into discontinuous patchy regions denoting an unstable tear film (85, 86).

Clinical Applications in Ocular Allergy
Seventy-eight percent of SAC patients were found to have an advanced tear instability and thickening of the tear film lipid layer with changes similar to those typical of dry eye (87).

Photography: Clinical evaluation of conjunctival hyperemia is subjective, and relies on grading scales ranging from 0-5 (88-90). Conjunctival hyperemia can be evaluated by the observer on the basis of digital photos using a modified grading scale or by using digital image analysis software. Digital image analysis is an objective evaluation method compared to the subjective evaluation by the investigators (91-96). Threshold-setting, edge-detection, color extraction, smoothing, fractal analysis or densitometry techniques are used in digital analysis.

Clinical Applications in Ocular Allergy
Assessment of symptom severity in allergy
Objectifying conjunctival provocation test (CAC Models)
Assessment of the efficacy of anti-allergic medications
Assessment of the efficacy of immunotherapy

Recommendations

- Emerging imaging technologies have potential roles in evaluating ocular surface changes in OA.
- New techniques may enable the clinician to estimate the degree of the inflammation helping in better diagnosis, follow-up and treatment of allergic process.
- Future widespread employment of these techniques supplementary to the routine examination techniques is of utmost importance.

Unmet needs in the diagnostic tools

- Specific questionnaires on medical history for ocular allergy
- It is still not clear why the eye can be the only target organ, or why some patients suffer from severe untreatable or chronic forms
- Specific mediator and cellular mechanisms associated with particular types of OA must be identified to lead to new diagnostic tools and novel therapies

- ….

Diagnostic algorithm
All
To be discussed and prepared at the two-days meeting

Concluding Recommendations
Table xxx

Tables

Table 1. Clinical features of major ocular allergy syndromes, including the underlying hypersensitivity mechanism and ophthalmological presentation (Allergy 2012).

	SAC	PAC	VKC	AKC	GPC	CBC
Presentation	Intermittent	Persistent	Persistent ± intermittent exacerbations	Chronic	Persistent	Chronic ± intermittent exacerbations
Allergic Mechanism	IgE-mediated	IgE-mediated	IgE and non-IgE-mediated	IgE- and non-IgE-mediated	Non allergic	Non-IgE-mediated
Background	Atopic	Atopic	Childhood ± atopic	Adult atopic	Atopic or non-atopic	Non-atopic
Eyelids	-	± Palpebral edema	Eyelid edema	Eczema + meibomitis blepharitis	-	Erythema, eczema
Conjunctiva	Follicles &/or papillae	Follicles &/or papillae	Giant papillae	Papillae ± fibrosis	Giant papillae	± Hyperemia Follicles
Limbus	-	-	± Thickened + Tranta's dots	± Thickened ± Tranta's dots	Hyperemia	-
Cornea	-	-	SPK ± Ulcer ± Vernal plaque	SPK Ulcer, Plaque, Opacities, neo-vascularization	Rare	-

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.

Table 2

Biblio search

Table 2 Relevant signs related in clinical ocular examination

Sign	Sign of Severity	Positive association with OA	Form of OA	Non allergic forms/ Differential diagnosis
Signs assessable by a non ophthamologist				
Conjunctival redness			All	Non allergic conjunctivitis, (epi)scleritis, keratitis, uveitis
Conjunctival giant papillae	Yes	++++	VKC, AKC	GPC
Limbal inflammation	Yes	++++	VKC, AKC	Limbal tumor
Chemosis, lid edema		+	All	Non allergic conjunctivitis
Mucus discharge		++	All, especially VKC, AKC	Infection, severe dry eye, GPC
Lid eczema		++++	AKC, CBC, VKC	Seborrhoeic dermatitis, psoriasis, lid molluscum
Blepharitis			All	Rosacea, seborrhoeic dermatitis
Signs only assessable by an ophthamologist				
Conjunctival papillae		+++	All	Bacterial conjunctivitis, rosacea, dry eye
Conjunctival follicules			All, especially CBC	Viral or chlamydial conjunctivitis, Parinaud's oculoglandular syndrome
Superficial punctate keratopathy, corneal scars, pannus	Yes		VKC, AKC	Non allergic keratitis
Corneal shield ulcer or plaque	Yes	++++	VKC, AKC	None
Tear instability			PAC > AKC, VKC	Rosacea, non allergic tear instability

OA= Ocular allergy; SAC=seasonal allergic conjunctivitis; PAC= perennial allergic conjunctivitis; VKC= vernal keratoconjunctivitis; AKC= atopic keratoconjunctivitis; GPC= giant papillary conjunctivitis; CBC= contact blepharo conjunctivitis

Table 4. Scoring system in ocular allergy (including CPT)

Itching
0 = none
1 = mild (intermittent itching sensation)
2 = moderate (continual awareness but without the desire to rub)
3 = severe (continual awareness with the desire to rub the eyes)
4 = incapacitating itching (subject insists on rubbing eyes).

Redness
0 = none
1 = mild (perhaps localized within some quadrant)
2 = moderate (more marked and diffuse reddening in the quadrants)
3 = severe (very marked and diffuse reddening in the quadrants).

Tearing
0 = none
1 = mild (slightly humid eye)
2 = moderate (some tears, blows nose occasionally)
3 = severe (profuse tearing, tears rolling down cheeks)

Chemosis
0 = none
1 = mild (detectable with slit lamp, conjunctiva raised from sclera)
2 = moderate (visually evident, raised conjunctiva, especially at the limbal area)
3 = severe (ballooning of conjunctiva)

Corneal Ulcer
grade 1: ulcers that extend the Bowman's membrane and yet have a transparent base
grade 2: ulcers that have an opaque base and are partially filled with inflammatory debris
grade 3: ulcers filled with debris (plaque) that remain above the surrounding epithelium

Table xxx. Recommendations for diagnostic tools in ocular allergy (draft #2)
Check Rec in each chapter

	Aims	Methods /Instruments	Recommendations
History	Evaluation of: -Symptoms and severity -Co-morbidities and general -Medical condition -Medical/surgical history -Exposure to allergens/ irritants/ non specific triggers -Visual tasks	-Talk to patients and parents -Questionnaires	•Accurate medical and personal history •Red eye differential diagnosis •Always ask for ocular signs and symptoms in other allergic co-morbidities •Investigate triggers for signs and symptoms •Refer to ophthalmologist (red eye DD)
QoL	-To assess the effects of disease on daily functioning, work, leisure and school perceived by patient	-Questionnaires	•Consider an assessment of impact of ocular allergy on QoL, however a specific questionnaire is missing •The EuroQoL (EQ-5D) gives at least the basic information on general QoL •In the absence of a specific questionnaire on ocular allergy the miniRQLQ can be used •The QUICK is the only specific and validated questionnaire for VKC
Ocular Examination	-To assess specific and non specific signs	-Observation with and without the slit lamp	
Visual function	-To assess best VA	-Optotypes	•Consider VA assessment as a primary outcome in daily practice •VKC and AKC subjects should undergo topographic corneal examination to rule out keratoconus
S&S Scores	evaluation of: -severity of the disease -CPT and NOT response -efficacy of treatments	-grading syspems	
Allergy Test	-Evaluation of the specific sensitization state and	-Skin prick test -Blood analysis with allergen-specific IgE -PATCH test	-Recommended in all patients with clinical suspicion of IgE allergic disease -Recommended in all patients with clinical suspicion of contact and eyedrop allergy
Conjunctival Provocation Test	-Evaluation of the conjunctival response to specific allergens	-Provocation by topical allergen at fixed solutions	-In case of negative SPT /sIgE -Polysensitized patients -To evaluate desensitization
Tear film function	-Evaluate tear film stability, quantity and dynamic	-BUT -Fluorescein staining -Shirmer test -Meibomian gland -	-In all patients with chronic allergy -When adverse environment cause symptoms
Ocular sampling	-Obtain tear fluids, cells, tissues for analysis	-Tear collection -Scrapings -Brush -Impression cytology -Biopsy	-Cytology for qualitative inflammation -In experimental and clinical studies -Biopsy in case of autoimmune diseases and unilateral/malignant disease
Tear Biomarkers	-Disease biomarkers -Severity biomarkers -Prognostic biomarkers	-ELISA -RIA -Omics	-Diagnostic tools in severe cases -
Imaging	-To evaluate corneal cells, nerves and stroma -Blood cell dynamics in conjunctiva -Meibomian glands	-Confocal microscopy Meibography -Photography	- -In experimental and clinical studies

Annex 1.
RC-ACS Symptom score

- 7 symptoms
  - 3 ocular: itching, tearing, redness
  - 4 nasal: sneezing, itching, running, blockage

- Scale ranging from 0 to 3:
  - 0 = absent (no sign/ symptom evident)
  - 1 = mild (sign/symptom clearly present, but minimal awareness; easily tolerated)
  - 2 = moderate (definite awareness of sign/symptom that is bothersome, but tolerable)
  - 3 = severe (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

The maximum total number of "score points" (SP) for symptoms on one day is 21 (7 x 3)

Rhino-Conjunctivitis Allergy-Control-Score (RC- ACS)

Annex 2

RC-ACS Medication score

Categories of medication included:

- Nasal medication:
  - anti-histamines, glucocorticoids, decongestants, mast cell stabilizers, and salts
- Ocular medication:
  - anti-histamines, mast cell stabilizers, decongestants, glucocorticoids, lubricants
- Systemic medication:
  - antihistamines, glucocorticoids and their combinations, leukotriene receptor antagonists.
- Drugs not foreseen by international Guidelines for treating allergic rhino-conjunctivitis are not included (e.g. anti- IgE)

The total SP for medication is also 21:

–nose sub-score (max. 12 SP)
–eyes (max. 9 SP)

Rhino-Conjunctivitis Allergy-Control-Score (RC- ACS)
The total number of "score points" (SP) for medication is also 21, subdivided into the two sub-scores for nose (max. 12 SP) and eyes (max. 9 SP)

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