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Allergic conjunctivitis: a cross-sectional study

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Abstract

Background. Ocular allergy is a common disease in daily practice.

Objectives. A cross-sectional study was conducted to evaluate clinical aspects of and therapeutic approaches to ocular allergy in Italy.

Methods. Of the 3685 patients affected by ocular allergy and enrolled by 304 ophthalmologists nationally, 3545 were eligible to be included in the statistical analysis. A questionnaire was administered in-office to record demographic data, co-morbidities, trigger factors, number of conjunctivitis episodes and past treatments. Signs and symptoms were graded according to their severity, frequency and duration.

Results. Mean age of enrolled patients was 38 ± 19 years. Seasonal allergic conjunctivitis (55% of patients) was equally distributed among the different age groups, while perennial allergic conjunctivitis (18%) increased with age and vernal keratoconjunctivitis (9%) was more frequent under the age of 18. Itching and redness were reported in 90% and 85%, respectively; lid skin involvement was observed in 22% of cases, and keratitis in 11%. Pollen sensitivities were indicated as the most frequent triggers, however, exposure to non-specific environmental conditions, pollutants and cigarette smoke was frequently reported. Only 35% of patients underwent a diagnostic evaluation of specific allergic sensitization, with positive allergy tests found in 82% of this subset. With regard to treatment, topical decongestants were used in 43% of patients, corticosteroids in 41%, antihistamines in 29%, systemic antihistamines in 27%, and mast cell stabilizers in 15%.

Conclusion. This survey provided useful epidemiological information regarding the clinical characteristics and treatment options of a large cohort of patients affected by different forms of ocular allergy.

Clinical relevance. An understanding of ocular allergic disease, its incidence, demographics and treatment paradigms, provides important information towards understanding its pharmacoeconomics and burden on the national health system.

Key words: allergic conjunctivitis, questionnaire, signs and symptoms, survey, treatment

INTRODUCTION

Allergic rhinitis and allergic rhinoconjunctivitis are common allergic disorders estimated to affect up to 40% of the population worldwide [1]. The prevalence of ocular allergies in the general population is estimated to be up to 40% in the United States [2] and up to 35% in Europe and the Middle East [3]. These data suggest a high comorbidity of conjunctivitis and rhinitis, although in ophthalmic practice the incidence observed is necessarily skewed toward the former. Whether ocular allergies are observed with or without rhinitis, this group of disorders significantly impacts quality of life [4-6]. The prevalence of allergic conjunctivitis has been difficult to establish and probably underestimated in most epidemiologic studies, since conjunctival symptoms are often not spontaneously reported in medical interviews or in questionnaire-based epidemiologic studies targeting rhinitis and/or asthma (8-10).

A new classification of ocular surface hypersensitivity disorders has been proposed based on and combining ophthalmology and allergy (ARIA) pathophysiology criteria [7]. According to the ARIA (Allergic Rhinitis and its Impact on Asthma) document [1], symptoms should be considered as intermittent or persistent; and mild, moderate or severe according to their evolution and severity. However, these concepts have not yet been consistently introduced into clinical practice nationwide [8].

The clinical signs and symptoms of ocular allergy are easily identified, and include itching, tearing, conjunctival hyperemia, and chemosis (edema). In the present study, we aimed to characterize the clinical and demographic aspects of allergic conjunctivitis seen in ophthalmologic settings using a validated questionnaire. A cross-sectional study surveying consecutively recruited patients with the

diagnosis of ocular allergy and observed in ophthalmology outpatient departments was conducted in Italy during the spring-summer of 2012. A simple structured questionnaire was administered in order to better define the clinical course of the disease and to introduce a standardized means of grading ocular signs and symptoms, establishing criteria for the severity, frequency and duration of ocular allergic episodes.

METHODS

Study design and participants

Patients were recruited by 304 ophthalmologists, in central or regional hospitals representative of the different geographic regions in Italy. Patients presented for treatment or follow-up of ocular allergy in ophthalmology outpatient services during the five-month study period (March to July 2012). For inclusion, all patients had to have a presumed diagnosis of ocular allergy based on the clinical signs and symptoms and slit lamp examination of the participant ophthalmologists. Each ophthalmologist consecutively recruited up to 20 patients during the study period. Patients or their parents gave their signed informed consent to participate in the survey. A specific, structured questionnaire (Appendix I) was administered to each recruited patient, characterizing nine eye signs and symptoms (itching, redness, photophobia, tearing, eyelid swelling, eye lid dermatitis, follicles, papillae and keratitis) by their severity (absent, mild/moderate, severe), frequency ($\leq$ than 4 episodes / week or $>$ than 4 episodes/ week) and duration during the previous year ($\leq$ than 4 weeks or $>$ than 4 weeks). The number of episodes of ocular allergy that had occurred in the previous year (1 to 5, 6 to 9, or more than 10 episodes) was recorded. If performed, positive results to skin prick tests and/or serum specific IgE to pollens, mites, animal, and food allergens were reported. Co-morbidity with other allergic manifestations and factors subjectively presumed to trigger ocular allergic episodes were also recorded.

Based on clinical history and signs and symptoms, the ophthalmologists were asked to categorize patients into one of six ocular allergy forms [8]: seasonal or intermittent allergic conjunctivitis (SAC), perennial or persistent allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), giant papillary conjunctivitis (GPC) and contact blepharoconjunctivitis (CBC). The treatment of the previous episode of conjunctivitis was also reported, dividing topical drugs into antihistamines, mast cell stabilizers, decongestant, decongestant and antihistamine combination, corticosteroids, corticosteroids and antibiotic combinations, antibiotics and systemic antihistamines.

Descriptive statistics were used and categorical variables summarized in terms of frequencies, percentages, means and standard deviations when appropriate.

RESULTS

Demographics

A total of 3685 patients were enrolled from 304 ophthalmology centers across different geographic regions in Italy (39% from the north; center 25% from the central region; and 36% from the south and islands).

Out of 3685 records, 3545 were evaluable and included in the analysis. The mean age of enrolled patients was 38.2 ± 19 years; 55.7% were female. The mean number of patients included by each doctor was 12 ± 3 . No significant differences were found in the prevalence of the different ocular allergic forms in the three Italian geographical regions. SAC was the most frequently reported diagnosis, followed by PAC, VKC and AKC (Figure 1). Both SAC and AKC were equally distributed among the different age groups, while PAC increased with age and VKC was typically more frequent, but not exclusively under age of 18. Considering the 603 patients under the age of 18 years, 133

(22%) were diagnosed with VKC. GPC (4% of patients) was more frequent in the 18-30 years of age group, and CBC (7%) was more frequent over 45 years of age.

A positive family history of allergy was reported in 43% of patients. PAC was the most frequently associated with family history of atopy (57%), followed by VKC (53%), SAC (40%), AKC (39%), GPC (38%), and CBC (25%).

Only 40% of patients reported a history of other allergic manifestations, such as rhinitis, asthma and dermatitis. The frequencies of associations in these patients are reported in Table 1. Comorbidity with other allergic diseases was reported in 58% of PAC patients, 43% of VKC patients, 41% of AKC, 36% of CBC, 34% of SAC, and 33% of GPC. Rhinitis was more frequently associated with SAC, PAC, and VKC, while dermatitis was more frequently associated with AKC and CBC (Table 1).

Eye symptoms and severity

A total of 68% of patients reported less than five episodes of conjunctivitis in the previous year, and 6% of patients reported more than 10 episodes (Table 2). Notably, 25.7% of patients reported that the current ocular allergic episode was the first.

Considering the entire patient population, itching was reported in 90.3% of cases (64.9% mild/moderate, 25.4% severe), redness in 84.6% (65.7% mild/moderate, 18.8% severe), tearing in 76.5% (58.6% mild/moderate, 17.9% severe), follicles in 42.2%, papillae in 47.5%, and keratitis in 11% (1.1% severe) (Figure 2). Considering each ocular allergic disease separately, in SAC, redness and itching were the predominant signs and symptoms, present in 85% and 92% of cases, respectively, but they were graded as severe only in 12% and 20% of cases. Follicles and papillae were reported in less than 40% of SAC patients, while keratitis was almost absent in this cohort.

Conversely, in PAC, follicles and papillae were present in almost 50% of patients. In AKC, in addition to the typical signs and symptoms of redness and itching, which 25% of patients graded as severe, the eye lid skin was involved in 37% of patients, and the cornea in 38% of patients. In VKC, itching and redness were present in 90% of patients, tearing in 86%, photophobia in 80%, papillae in 75%, and keratitis in 30%. The main symptom, itching, was present in 90% of the entire patient population: its duration in each disease is shown in Table 3. Considering the severity of signs and symptoms in relation to the their frequency and duration, severe itching, redness, photophobia and tearing more than four times/week and for more than four weeks, were reported in 25% of the entire patient population (Table 4). Severe and persistent papillae were reported in 22% of patients, severe and persistent eyelid dermatitis in 17%, and severe and persistent keratitis in 8% of cases.

Trigger factors

Pollen was reported as the most frequent trigger, however, exposure to non-specific environmental conditions, pollutants and cigarette smoke was also frequently reported (Table 5). Only 20.5% of the patients reported a single factor as the primary trigger of conjunctivitis.

Diagnosis

Only 35% of patients (1240) underwent a diagnostic evaluation of allergic sensitivities. Results of skin prick test and/or specific serum IgE were positive in 82.6% (1024) of this subset, with some differences noted among diseases (Table 6). In patients with co-morbidities, allergy tests were performed in 59.3%, and resulted positive in 97.7%.

Treatment options

A total of 2687 patients (75.8%) had previously used one or more medications for the treatment of ocular allergy; 60% of patients reported using two or more medications. Over the counter decongestant/antihistamines were used in 43% of cases, corticosteroids in 41%, topical antihistamines in 29%, systemic antihistamines in 27%, mast cell stabilizers in 15% and antibiotics in 6% of cases. Interestingly, mast cell stabilizers were used in 11% of SAC, 21% of PAC, 25% of VKC and 18% of AKC, while corticosteroids were used in 67% of GPC, 55% of VKC, 53% of AKC, 47% of CBC, in 43% of PAC and 28% of SAC.

DISCUSSION

This is one the largest surveys performed at a national level that has focused specifically on ocular allergy, involving the specialist that directly evaluated eye signs and symptoms and performed a differential diagnosis. Although this is not an epidemiological study, it reflects the impact of allergic patients on ophthalmology centers and the Italian health system, as well as use patterns for treatment. The prevalence of the different ocular allergic diseases has some variation between different geographic areas of the world not only due to genetic differences and environmental factors, but also due to the lack of standardization in the assessment of ocular symptoms [8].

To date, the epidemiology of ocular allergy is based on allergic rhinoconjunctivitis (ARC) studies performed by non-ophthalmologists. However, the classification of ocular allergy includes other, certainly less frequent, conditions that require an ophthalmological evaluation for diagnosis [8]. In the ARIA document, seasonal and persistent ARC affect 3-42% and 1-18% of the population, respectively, depending on different climatic conditions and age groups [1]. In the National Health and Nutrition Examination Survey, with a sample size of 20,010 in the U.S., 40% of cases reported at least one ocular allergy symptom [2]. Ocular allergy has been reported to be twice as common as

allergic rhinitis [9], and the prevalence of PAC seems to be underestimated by both ophthalmologists and allergists [10]. PAC is known to be more associated with a mite sensitivity, and thus, not surprisingly, comorbidity with allergic rhinitis has been reported in 46% of patients [11]. In the present Italian cohort, only 40% of PAC patients had an associated non-ocular allergic condition. We and others previously reported that there is a large population of patients with only ocular symptoms [9] and with only local tissue allergen sensitivity [12]. Therefore, it is quite common that patients with ocular allergic symptoms request an ophthalmological evaluation before an allergy consultancy. In fact, 25% of patients reported that the purpose of the ophthalmologic visit was indeed the first episode of conjunctivitis, and 68% of patients reported having had one to five episodes of conjunctivitis/year.

Although only 35% of patients included in this survey underwent specific allergy testing, ophthalmologists were able to successfully diagnose the 3545 patients as affected by one of the six ocular allergic conditions defined in the questionnaire. In fact, the diagnosis of ocular allergy is relatively simple and is based mostly on clinical history, signs and symptoms, which may or may not be confirmed by the results of allergy tests [8]. The tests were requested more frequently in PAC, probably because it is more difficult to diagnose due to the lack of specific clinical signs, and its non-seasonality. Similarly, a study performed in Portugal on 220 patients with allergic conjunctivitis, demonstrated that 19% had an appointment with an ophthalmologist as “a first action” and only 37% of the cohort had a previous allergic evaluation [6].

A simple questionnaire may help to ask the proper questions to the patients to better highlight not only signs and symptoms but also their frequency, duration and severity. The Ocular Surface Disease Index (OSDI) is a valid and reliable instrument for assessing the subject's perception of dry eye disease (normal, mild to moderate, and severe) and its effect on vision-related function. A health-related quality of life questionnaire has been developed and proposed for VKC children [13]. A validated questionnaire on symptoms was used in adolescents to diagnose allergic conjunctivitis [14],

however, no signs and ophthalmological evaluations were included. In the present survey, we observed that 70% of patients had only a few episodes of mild conjunctivitis annually, but 30% of patients had frequent episodes with intense and persistent symptoms. As expected, the vast majority of patients reported itching and redness as the main symptoms, but a quarter of them had severe signs and symptoms more than four times per week and for more than 4 weeks in duration. Keratitis was reported to be severe and persistent in almost 10% of patients, suggesting that clinical corneal involvement is not as uncommon as thought in ocular allergic patients.

The estimated prevalence of VKC in Europe is 3.2/10,000, whereas it is almost endemic in subtropical countries [15, 16]. Warm climates and sun exposure probably explain the characteristic north-south gradient of prevalence. In the present cohort, VKC comprised 8% of ocular allergies, and 22% of patients under the age of 18 years. The finding of a consistent percentage of VKC patients over the age of 18 confirms our recent description of a VKC-like disease with adult onset [17], as well as inclusion of a number of VKC patients who have recurrences after puberty.

Regarding treatment options, interestingly both decongestants and corticosteroids were used in more than 40% of cases, independently from specific diagnosis, while antihistamines and mast cell stabilizers were used less frequently. These trends do not follow recommendations for the treatment of ocular allergies [8, 18]. Considering that the most frequently diagnosed diseases were the typical IgE-mediated forms, SAC and PAC, which are dependent on specific mast cell activation and histamine release, the treatments reported might not have been ideal. Antihistamines and mast cell stabilizers might still not be prescribed by primary care ophthalmologists as the first choice of treatment, and also many allergic patients might treat themselves with topical vasoconstrictors that provide rapid relief from redness and congestion. Vasoconstrictors are indicated for the temporary relief of itch and redness but have a short duration of action and are associated with the risk of local and systemic side effects [19]. Nevertheless, in some cases, prophylactic combinations such as

pheniramine/naphazoline have been found to be more effective and preferred by patients than olopatadine in alleviating the signs and symptoms of the acute ocular allergic reaction induced by conjunctival allergen challenge [20]. Topical corticosteroids should be avoided in SAC and PAC, but are indicated for the treatment of severe and chronic forms of keratoconjunctivitis, which affected approximately 15% of patients in the present cohort.

In conclusion, this survey based on a simple questionnaire has provided extremely useful information regarding the clinical characteristics and treatment options of a large cohort of patients affected by different forms of ocular allergy.

Figure Legends

Figure 1. Percentage of patients diagnosed with a specific ocular allergic disease. SAC= seasonal allergic conjunctivitis; PAC = perennial allergic conjunctivitis; AKC= atopic keratoconjunctivitis; VKC= vernal keratoconjunctivitis; CBC= contact blepharoconjunctivitis; GPC= giant papillary conjunctivitis.

Figure 2. Presence and severity of signs and symptoms in the entire population of allergic conjunctivitis patients: itching was reported in 90% of patients, redness in 85%, photophobia in 65%, tearing in 26%, lid swelling in 37%, follicles in 42%, papillae in 47%, keratitis in 11% .

Table 1. Co-morbidities of allergic conjunctivitis (data expressed in % of patients).

Allergic disease	Total	SAC	PAC	VKC	AKC	GPC	CBC
Rhinitis	45.3	55.9	40.4	46.2	25.0	35.4	19.4
Asthma	16.4	15.0	20.5	16.2	14.5	25.0	9.7
Dermatitis	17.7	13.2	15.2	17.7	37.5	22.9	54.8
Rhinitis + Asthma	12.2	10.1	13.3	9.2	7.3	8.3	4.8
Rhinitis + Dermatitis	4.7	3.8	6.1	4.6	7.3	2.1	6.5
Asthma + Dermatitis	1.7	0.8	2.4	2.3	4.2	2.1	3.2
Rhinitis + Asthma + Dermatitis	2.0	1.2	2.1	3.8	4.2	4.2	1.6

Table 2. Number of recurrences of conjunctivitis in the last 12 months

Number of episodes of conjunctivitis /year	%
1 to 5	68.2
6 to 9	25.2
> 10	6.6

Table 3. Duration of the main symptom itching for each ocular disease (data expressed in % of patients)

	≤ than 4 weeks	> than 4 weeks
SAC	77.8	22.2
PAC	46.7	53.3
VKC	57.2	42.8
AKC	66	34
GPC	54.5	45.5
CBC	69.9	30.1

Table 4. Frequency and duration of the main symptoms (itching, redness, photophobia and tearing) by the severity of the disease in the total patient population (data expressed in % of patients).

Severity	Frequency	Duration <4 weeks (68.6)	Duration >4 weeks (31.4)
Mild / moderate (75)	(67.7) ≤ than 4 episodes/ week	87.7	12.3
	(32.3) > than 4 episodes/ week	46.6	53.4
Severe (25)	(35.2) ≤ than 4 episodes/ week	77.3	22.7
	(64.8) > than 4 episodes/ week	37.3	62.7

Table 5. Subjective trigger factors of allergic conjunctivitis

	More than One Factor		Single Factor	
	Number of trigger factors in 2817 patients	%	Number of patients (728)	%
Pollens	2433	25.0	369	50.7
Dust	1858	19.1	94	12.9
Animals	892	9.2	50	6.9
Sun / wind/ light	1753	18.0	113	15.5
Pollutants	1201	12.3	68	9.3
office /personal computer	540	5.5	20	2.7
Stress	465	4.8	10	1.4
Smoke	594	6.1	4	0.5

Table 6. Reported positive results to the allergy tests (data expressed in % of patients).

Allergens	Total	SAC	PAC	VKC	AKC	GPC	CBC
Pollens	31.3	49.7	14.4	27.4	9.3	10.9	10.6
Mites	8.7	4.0	16.2	11.3	15.6	2.7	2.6
Pets	3.4	2.1	2.1	4.7	1.6	5.4	28.9
Food	3.8	2.7	3.5	0.9	7.8	8.1	18.5
Pollens + Mites	25.2	21.7	35.5	32.1	14.1	18.9	15.9
Pollens + Food	2.6	4.1	0.4	1.9	1.6	5.4	2.6
Pollens + Pets	2.3	3.1	2.1	0	3.1	0	2.6
Mites + Pets	4.3	2.9	8.7	1.9	4.7	5.4	2.6
Mites + Food	1.6	0.6	0.2	0	6.2	2.7	2.6
Pets + Food	0.7	0	1.1	0.9	7.8	0	2.6
Pollens + Mites + Pets	8.7	4.8	3.6	9.4	17.2	13.5	2.6
Pollens + Mites + Food	2.9	1.2	3.9	5.7	1.6	8.1	7.9
Pollens + Pets + Food	0.5	0.4	3.6	0	1.6	5.4	0
Mites+ Pets + Food	0.5	0.2	1.1	0	1.6	0	0
Pollens + Mites + Pets + Food	3.5	2.4	3.6	3.8	6.2	13.5	0

Table 7. Length of treatments for the last episode of conjunctivitis

Days	Number of Patients	%
1-7	678	27.3
8-14	852	34.4
15-21	532	21.5
>21days	418	16.9
Total	2480	100.0

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Critical revision of the article: PM, IF, DL

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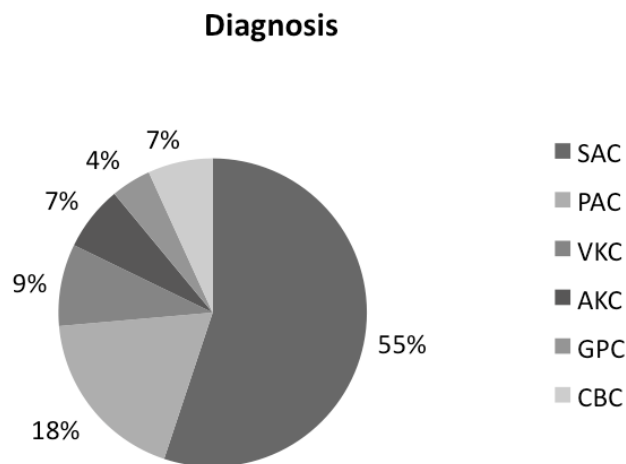
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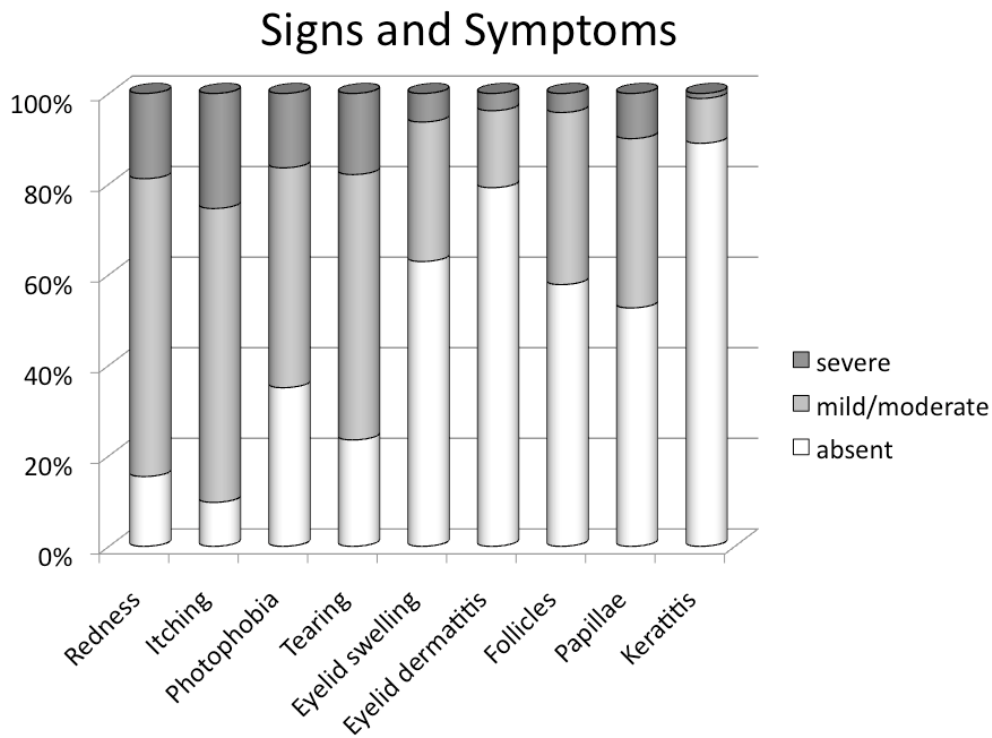
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Appendix I

Allergic Conjunctivitis – ITALIAN SURVEY 2012

PATIENT (initials): _____

(Age) Date of birthday: _____ SEX: M ☐ F ☐

Month of the visit: _____

Geographical area: Nord ☐ Center ☐ South and Islands ☐

SIGNS AND SYMPTOMS

	INTENSITY			FREQUENCY*		DURATION**	
	None	Mild / moderate	Severe	1	2	3	4
Redness	☐	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐	☐
Photophobia	☐	☐	☐	☐	☐	☐	☐
Tearing ☐	☐	☐	☐	☐	☐	☐	☐
Lid swelling	☐	☐	☐	☐	☐	☐	☐
Lid dermatitis	☐	☐	☐	☐	☐	☐	☐
Follicles	☐	☐	☐	☐	☐	☐	☐
Papillae ☐	☐	☐	☐	☐	☐	☐	☐
Keratitis	☐	☐	☐	☐	☐	☐	☐

DIAGNOSIS

SAC (1) ☐ PAC (2) ☐ AKC (3) ☐ VKC (4) ☐ GPC (5) ☐ CBC (6) ☐

Frequency and duration

* (1) Less than 4 episodes per week

(2) More than 4 episodes per week

** (3) Less than 4 weeks

(4) More than 4 weeks

(1) SAC: Seasonal (intermittent) allergic conjunctivitis

(2) PAC: Perennial (persistent) allergic conjunctivitis

(3) AKC: Atopic keratoconjunctivitis

(4) VKC: Vernal keratoconjunctivitis

(5) GPC: Giant papillary conjunctivitis

(6) CBC: Contact blepharo conjunctivitis

CONJUNCTIVITIS RECURRENCES AND TREATMENT

Is this the first episode of conjunctivitis? YES ☐ NO ☐

Did you have other episodes in the last 12 months? YES ☐ NO ☐

If YES, how many in the last 12 months? 1 ☐ (1 to 5) 2 ☐ (6 to 10) 3 ☐ (>10)

Did you use drugs for the conjunctivitis? YES ☐ NO ☐

If YES, which one?

Antibiotics ☐ Systemic Antihistamine ☐ Topical Antihistamine ☐

Mast cell stabilizer ☐ Topical corticosteroids ☐ Topical corticosteroids + antibiotics ☐

Topical Decongestant ☐ Topical Decongestant + antihistamine ☐

Length of treatment? (also multiple)

1 ☐ (0-7 days) 2 ☐ (8-14 days) 3 ☐ (15-21 days) 4 ☐ (>22 days)

HISTORY AND DIAGNOSTIC TESTS

Family history for allergy? YES ☐ NO ☐

Other allergic diseases? YES ☐ NO ☐

If YES, which one?

Rhinitis ☐ Asthma ☐ Dermatitis ☐

Performed allergy tests (skin prick test/ serum IgE) YES ☐ NO ☐

If YES, positive to?

Pollens ☐ Mites ☐ Animals ☐ Food ☐

TRIGGERS

Which factor(s) do you believe trigger your episodes (subjective)?

Pollens (outdoor environment)

YES ☐ NO ☐

Dust (mites)

YES ☐ NO ☐

Animals

YES ☐ NO ☐

Pollution

YES ☐ NO ☐

Sun/Wind/Light

YES ☐ NO ☐

Office/ computer

YES ☐ NO ☐

Stress

YES ☐ NO ☐

Smoke

YES ☐ NO ☐

Date _____

Doctor's signature _____