

Managing ocular allergy in the time of COVID-19

To the Editor

This spring, the majority of allergic patients are confined to their homes due to COVID-19 pandemic restrictions. In the following weeks, these restrictions will be reduced and people will be allowed to take walks, go jogging, and return to work. Spring is the time for ocular allergy (OA) to emerge with signs and symptoms consequent to increasing pollen counts. Even when wearing a mask, the eyes may remain unprotected leading to an increase in ocular symptoms and patients seeking treatment for OA. However, access to routine consultation may remain problematic for many patients.

Diagnosis and management of allergic rhinoconjunctivitis is a common practice for allergists, pediatricians, rhinologists, ophthalmologists, and general practitioners. They are used to manage the most common forms of OA such as seasonal and perennial allergic conjunctivitis (SAC and PAC). The management of severe forms

such as vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), which can result in corneal complications and cause sight-threatening sequelae, requires specialized expertise.¹ VKC and AKC may require repeated courses of topical corticosteroids and/or long-term use of topical immunomodulators. Immunosuppression, even localized to the ocular surface through the topical use of cyclosporine and tacrolimus, has the potential to increase susceptibility, persistence, and reactivation of any viral infection. Although the presence of SARS-CoV-2 in tears has rarely been detected in infected individuals,^{2,3} conjunctivitis may be a sign of COVID-19, prior to or after the onset of respiratory symptoms.⁴

Recommendations on the management of OA were recently published by the EAACI working group on OA (WG-OA).⁵ Considering the numerous problems due to the COVID-19 pandemic, including the health system crisis and limited access to consultants, we were

TABLE 1 Treatment options for SAC

Topical antiallergic drops					
SARS-CoV-2 infection	Agree	Partially agree	Partially disagree	Disagree	No opinion
Not at risk, n (%)	28 (93%)	1 (3%)	0	0	0
At risk, n (%)	29 (97%)	0	0	0	0
Current infection, n (%)	29 (97%)	0	0	0	0
Previous infection, n (%)	28 (93%)	1 (3%)	0	0	0
Low-dose topical corticosteroids in case of no response					
Not at risk, n (%)	14 (47%)	10 (33%)	1 (3%)	3 (10%)	0
At risk, n (%)	10 (33%)	6 (20%)	1 (3%)	12 (40%)	0
Current infection, n (%)	9 (30%)	4 (13%)	3 (10%)	13 (43%)	0
Previous infection, n (%)	13 (43%)	10 (33%)	1 (3%)	6 (20%)	0
Only oral antihistamines					
Not at risk, n (%)	10 (3%)	2 (7%)	4 (13%)	11 (37%)	0
At risk, n (%)	8 (27%)	8 (27%)	3 (10%)	9 (30%)	1 (3%)
Current infection, n (%)	6 (20%)	4 (13%)	6 (20%)	11 (37%)	0
Previous infection, n (%)	8 (27%)	1 (3%)	7 (23%)	11 (37%)	0

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Topical antiallergic drops					
SARS-CoV-2 infection	Agree	Partially agree	Partially disagree	Disagree	No opinion
Not at risk, n (%)	26 (87%)	2 (7%)	0	0	0
At risk, n (%)	26 (87%)	0	1 (3%)	0	1 (3%)
Current infection, n (%)	26 (87%)	0	1 (3%)	0	1 (3%)
Previous infection, n (%)	25 (83%)	1 (3%)	1 (3%)	0	1 (3%)
Topical corticosteroids as needed as pulse therapy					
Not at risk, n (%)	26 (87%)	2 (7%)	0	0	1 (3%)
At risk, n (%)	15 (50%)	9 (30%)	1 (3%)	2 (7%)	1 (3%)
Current infection, n (%)	12 (40%)	7 (17%)	6 (20%)	4 (13%)	2 (7%)
Previous infection, n (%)	16 (53%)	10 (33%)	1 (3%)	1 (3%)	1 (3%)
Topical corticosteroids as needed at low dose but long term					
Not at risk, n (%)	6 (20%)	2 (7%)	6 (20%)	10 (33%)	1 (3%)
At risk, n (%)	2 (7%)	5 (17%)	6 (20%)	13 (43%)	1 (3%)
Current infection, n (%)	2 (7%)	2 (7%)	7 (23%)	14 (47%)	2 (7%)
Previous infection, n (%)	4 (13%)	2 (7%)	9 (30%)	10 (33%)	1 (3%)
Topical calcineurin inhibitors					
Not at risk, n (%)	20 (67%)	7 (23%)	1 (3%)	0	1 (3%)
At risk, n (%)	10 (33%)	10 (33%)	4 (13%)	2 (7%)	3 (10%)
Current infection, n (%)	8 (27%)	7 (23%)	5 (17%)	7 (23%)	2 (7%)
Previous infection, n (%)	14 (47%)	9 (30%)	1 (3%)	2 (7%)	3 (10%)

TABLE 2 Treatment options for VKC/AKC

wondering whether established guidelines are still applicable. This letter reports the results of a survey conducted by members of the WG-OA regarding the management of clinical forms of OA in the time of COVID-19.

Twenty members of the WG-OA and an additional 24 international experts in the field of ocular surface diseases were asked to complete a questionnaire using the Research Electronic Data Capture (REDCap) tool (Supporting information). Questions were closed-ended and focused on the management of SAC, VKC, and AKC. Treatment options were stated for SAC and VKC/AKC patients experiencing active ocular symptoms in different situations: (a) *not at risk* of SARS-CoV-2 infection; (b) *at risk* of SARS-CoV-2 infection; (c) *current* SARS-CoV-2 infection; and (d) with *previous* SARS-CoV-2 infection (for definitions, see Supporting information). Two additional questions focused on the management of refractory AKC that may require systemic intervention or immunosuppression. Responses were selected from a Likert scale with 5 options (agree, partially agree, partially disagree, disagree, and no opinion). In addition, recommendations for OA treatment were evaluated to confirm agreement with published data⁵ (Supporting information).

Results were obtained from 30 specialists, both from EU and other continents (18 ophthalmologists and 12 allergists). Their responses indicate that treatment options for SAC are still valid despite COVID-19-related problems (Table 1). The use of low-dose corticosteroids in case of no response was validated by the experts' responses except in patients at risk of or with current SARS-CoV-2 infection. Topical antiallergic eye drops were validated by all consulted specialists. The use of oral antihistamine only remains an acceptable option for some of the respondents.

Regarding VKC/AKC, topical antiallergic drugs remain definitively the first-choice treatment, with the addition of topical corticosteroids as the second-choice treatment (Table 2). Regarding patients with current infection, there is disagreement on the choice of topical corticosteroid regimen; 57% of the respondents will use them as pulse therapy, while 14% a slow dose for long term (Table 2). There is good agreement on the use of topical immunomodulators in severe VKC/AKC patients not at risk of infection (90% agree), lower for patients at risk (66%), or with current infection (50%), while 77% agreed to use them in patients with previous infection.

The use of systemic immunosuppressant for severe AKC patients not responding to topical treatment was definitely not a consensual decision even before COVID-19. We did not consider this question for patients with current SARS-CoV-2 infection because initiating immunosuppression in this case would be extremely rare and controversial. In severe, nonresponder AKC patients, the experts generally prefer local treatment in patients at risk (73%) and with previous infection (63%) (Table S1). The addition of systemic treatment/immunomodulation is not considered a good choice for patients at risk (most respondents disagreed or had no opinion), whereas in patients with previous infection, 50% of respondents recommended the addition of corticosteroids, 60% cyclosporine, 47% azathioprine, and 47% dupilumab. Furthermore, the present survey confirms that the recent EAACI WG-OA recommendations for the management of OA⁵ are well accepted and still valid in the time of COVID-19 (Table S2, Supporting information).

As expected, the survey highlights some caution regarding the use of topical calcineurin inhibitors in severe VKC/AKC patients at risk and with current infection despite the negligible systemic absorption of topical cyclosporine.⁶ Since eye rubbing is not recommended in any type of OA especially in time of COVID-19, we suggest not to stop calcineurin inhibitors in severe VKC children at risk, while in patients with current disease the decision should be taken case by case. The risk of encountering a SARS-CoV-2-positive VKC patient is low, since the prevalence of VKC is estimated to be 4/10 000 under the age of 15 in Veneto Region (Italy)⁷ and the prevalence of COVID-19 cases under the age of 14 is about 1.5% in the same area, which has been one of the most affected areas in Europe. These numbers may be even lower in most EU and non-EU countries but higher in areas, such as India and Africa, where VKC is more prevalent^{8,9} and inappropriate use of steroids may lead to vision-threatening complications. The use of systemic immunosuppression in severe AKC patients not responding to topical treatment remains a matter of debate that warrants case-by-case evaluation and multidisciplinary consensus.

The present survey was conducted within a panel of international ocular surface experts. The management of OA in the time of COVID-19 should still follow the EAACI recommendations.⁵ A particular caution is recommended for the use of corticosteroids and immunomodulators since a definitive consensus was not obtained, particularly for ongoing infected patients.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Managing ocular allergy in the time of COVID-19

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Definition of different situations at which patients may experience symptoms of ocular allergy.

At risk: in pandemic scenario theoretically all people are at risk of SARS-CoV-2 infection. However, at (higher) risk can be operationally considered: people over 60 years old; people with underlying medical conditions such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer; recent contacts with positive patients; positive cases in the family or at work place; health professionals

Current SARS-Cov-2 infection: all positive SARS-CoV-2 RNA test either symptomatic or asymptomatic until declared cured.

Previous SARS-Cov-2 infection: symptomatic cases, hospitalized, can be considered cured after the resolution of symptoms and 2 negative tests for SARSCoV-2 at 24-hour intervals by RT-PCR. Asymptomatic infections and persons isolated at home, negative SARS-CoV-2 RNA test at 14 days after the first test (end of the quarantine period).

[adapted from: www.ecdc.europa.eu › covid-19](http://www.ecdc.europa.eu/covid-19)

To complete the questionnaire, the Research Electronic Data Capture (REDCap) tool was used. REDCap is a metadata-driven software and workflow methodology for designing clinical and translational research databases. It is particularly devoted to multicentre surveys. Here it was hosted by the Department of Clinical Research in Clermont-Ferrand, France and conducted by an independent surveyor.

Tables S1 and S2

Table S1. Treatment options for systemic immunosuppression in refractory AKC

	Only topical treatment				
SARS-Cov-2	Agree	Partially agree	Partially disagree	disagree	no opinion
At-risk, n (%)	15 (50%)	7 (23%)	1 (3%)	5 (17%)	2 (7%)
Previous infection, n (%)	15 (50%)	4 (13%)	2 (7%)	6 (20%)	2 (7%)
	Add systemic corticosteroids at high dose				
At-risk, n (%)	3 (10%)	7 (23%)	6 (20%)	10 (33%)	2 (7%)
Previous infection, n (%)	8 (27%)	7 (23%)	7 (23%)	4 (13%)	2 (7%)
	Add systemic immunomodulation with cyclosporine				
At-risk, n (%)	5 (17%)	8 (27%)	3 (10%)	10 (33%)	2 (7%)
Previous infection, n (%)	8 (27%)	10 (33%)	3 (10%)	6 (20%)	2 (7%)
	Add systemic immunomodulation with azathioprine				
At-risk, n (%)	1 (3%)	4 (13%)	7 (23%)	12 (40%)	4 (13%)
Previous infection, n (%)	3 (10%)	11 (37%)	4 (13%)	7 (23%)	5 (17%)
	Add systemic immunomodulation with dupilumab				
At-risk, n (%)	2 (7%)	4 (13%)	5 (17%)	13 (43%)	5 (17%)
Previous infection, n (%)	6 (20%)	8 (27%)	6 (20%)	2 (7%)	6 (20%)

Table S2. Recommendations for ocular allergy treatment.

In the time of COVID-19 do you agree on the general recommendations for the management of ocular allergy? (Leonardi A, Silva D, Perez Formigo D, Bozkurt B, et al. Allergy. 2019;74(9):1611-30.)

A	How to treat IgE-mediated diseases SAC and PAC	agree/ partially agree/ partially disagree/ disagree/ no opinion
1	Avoidance of clinically relevant allergens is the first step in the prevention of ocular allergy symptoms	(29/0/0/0/0)
2	Topical antihistamines, mast cell stabilizers, or dual-action drugs are the first choice of treatment, and all effective in reducing signs and symptoms	(28/1/0/0/0)
3	Dual-acting agents with combined mast cell stabilizer and antihistaminic function increase the possibility of symptom improvement and have a faster relief of symptoms compared to mast cell stabilizers	(27/1/0/1/0)
4	Avoid topical corticosteroids, as they are rarely needed	(19/6/2/2/0)
5	Intranasal corticosteroids are effective and well tolerated in the treatment of ocular symptoms associated with ARC, but should not be used if only ocular signs and symptoms are present	(20/6/2/0/1)
6	Topical vasoconstrictors alleviate only hyperemia and should be used with caution for a short period of 5-7 days because of side effects and tachyphylaxis	(23/4/0/1/1)
7	Systemic antihistamines should be used in acute forms or when ocular symptoms are associated with other allergic comorbidities	(24/5/0/0/0)
8	Leukotriene inhibitors are reported to be less efficacious than oral antihistamines in adult SAC patients	(24/4/0/0/1)
9	Consider SIT when specific sensitization is the main cause of ocular allergy, as it is effective for the treatment of ARC to seasonal allergens and perennial allergens	(24/3/0/2/0)
10	SLIT has been shown to be effective in reducing total and individual ocular symptom score in subjects with conjunctivitis	(23/5/1/0/0)

B	How to treat persistent/chronic forms (IgE- and non-IgE-mediated) VKC and AKC	agree/ partially agree/ partially disagree/ disagree/ no opinion
1	Avoidance of specific and nonspecific triggers is the first step in the prevention of ocular allergy symptoms	(26/2/1/0/0)
2	Use cold compresses, good eyelid hygiene, and lubricants	(27/1/0/0/0)
3	Topical antihistamines, mast cell stabilizers, or dual-action drugs are the first treatment choice and may be used in combination. They should be used frequently during the day and during the whole season	(29/0/0/0/0)
4	Systemic anti-allergic drugs should be used when ocular symptoms are associated with other allergic comorbidities	(25/4/0/0/0)
5	Topical corticosteroids should be used as short, pulsed therapy, in acute exacerbations or when the cornea is involved, under ophthalmologist's monitoring	(27/1/0/0/1)

6	Topical calcineurin inhibitors, preferentially cyclosporine A (0.1% on-label treatment in the EU), may be used as a steroid-sparing agent in steroid-dependent patients followed in specialized centers; tacrolimus 0.1% eye drops should be reserved for severe VKC and AKC cases refractory to CsA (off-label treatment in the EU)	(21/6/1/0/1)
7	A systemic immunosuppressive treatment should be prescribed in most refractory cases of AKC with visual threat. Cyclosporine is the most frequently used drug. Tacrolimus and mycophenolate mofetil are alternative options	(18/8/20/1)