

DOI: 10.1111/all.14361

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 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

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

TABLE 2 Treatment options for VKC/AKC

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%)

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.


ACKNOWLEDGMENTS

We would like to express our gratitude to the responders to our survey: Shweta Agarwal (India), YoncaAkova (Turkey), EsenAkpek, (USA), Penny Asbell (USA), Christophe Baudouin (France), Arthur Baye (France), Stefano Bonini (Italy), Banu Bozkurt (Turkey), Dominique Bremond-Gignac (France), Gonzalo Chorzepa (Argentina), Luis Delgado (Portugal), Antonio Di Zazzo (Italy), Serge Doan (France), Murat Dogru (Japan), Jean-Luc Fauquert (France), Cecile His Gallego (France), Murat Irkec (Turkey), Connie Katelaris (Australia), SihemLazreg (Algeria), Andrea Leonardi (Italy), Farid Marmouz (France), Jesus Merayo (Spain), Ralf Moesges (Germany), Bruno Mortemousque (France), Jorge Palmares (Portugal), Daniel Perez Formigo (Spain), Oliver Pfaar (Germany), Carmen Rondon (Spain), Diana Silva (Portugal), and NilgünYıldırım (Turkey).

CONFLICT OF INTEREST

Dr Klimek reports grants and personal fees from Allergopharma, MEDA/Mylan, LETIPharma, and Sanofi; personal fees from

HAL Allergy and Allergy Therapeut.; grants from ALK Abelló, Stallergenes, Quintiles, ASIT Biotech, Lofarma, AstraZeneca, GSK, and ImmunoTek, outside the submitted work; and acts as a member of AEDA, DGHNO, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV GPA, and EAACI.

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SUPPORTING INFORMATION

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

DOI: 10.1111/all.14369

Allergy and asthma in children and adolescents during the COVID outbreak: What we know and how we could prevent allergy and asthma flares

To the Editor,

The coronavirus disease 2019 (COVID-19) pandemic is affecting people at any age with a more severe course in patients with chronic diseases or comorbidities, men, and elderly patients. The Centers for Disease Control and Prevention (CDC) initially proposed that patients with chronic lung diseases, including moderate-severe asthma, and allergy may have a higher risk of developing severe COVID-19 than otherwise healthy people (<https://www.cdc.gov/coronaviruses/2019-ncov/specific-groups/asthma.html>).

Very few reports on pediatric patients with COVID-19 have been presented still now. Dong reported a nationwide case series of 2143 pediatric patients with COVID-19.¹ Children at all ages appeared susceptible to COVID-19, and without gender difference, symptoms were less severe than in adults, even though younger children, mainly infants, were vulnerable to infection. It has been, further, reported that infants and children usually developed mild respiratory symptoms, or they were likely asymptomatic.² After that, a study conducted in 140 hospitalized COVID-19 adult patients reported that no patient had asthma or allergy.³ Another study, concerning 11 COVID-19 patients, reported two children with allergy, but no patient developed distinct symptoms and severe courses.⁴ These last reports were surprising and theoretically conflicting with the well-known paradigm by which viral infections worsen asthma and allergic diseases. As a result, we would verify this Chinese evidence in Italy. Italy was the first European country remarkably involved in the COVID-19 pandemic. The first cluster occurred in south Lombardy; then, the infection spread across Italy. We reported, therefore, the data concerning the patients referred for COVID-19 to two hub hospitals located respectively in south Lombardy (Policlinico San Matteo, Pavia) and Liguria (Istituto G. Gaslini, Genoa). Demographic and clinical outcomes are reported in Table 1.

About 2 3150 000 people live in south Lombardy and Liguria; the mean pediatric population is 14.5%, allergic children are more

than 30%, and asthmatic children are 11.6%. The total number of COVID-19 patients was 12 055 in both geographical areas on April 16; pediatric COVID-19 patients were respectively 18 and 22 (19 male, median age 5 years, interquartile range 1-12.5). The data are available on the website of the Istituto Superiore di Sanità (<https://www.epicentro.iss.it>). COVID-19 was diagnosed on clinical data and positive swab (RT-PCR analysis). The most common symptoms were fever (67.5%), cough (55%), nasopharyngeal complaints (27.5%), and gastrointestinal symptoms (17.5%). No child reported dyspnea, and 8 (20%) children were asymptomatic, anosmia/dysgeusia was present in only 3 (12.5%) subjects, and pneumonia was diagnosed in 4 (10%) children. Twenty-four (60%) children were hospitalized, but only one required oxygen therapy and ICU admission. These outcomes confirmed that COVID-19 in children is usually rare, mild-moderate, and without sex difference, but may affect any age. At present, pediatric COVID-19 concerns about 1% of the entire COVID-19 population. Several hypotheses have been prospected to explain the clinical feature observed in childhood, including the different frequency of ACE2 expression on pneumocytes, which is higher in the elderly and adult men. ACE2 is the receptor for coronavirus. Thus, overexpression may promote infection. Hypertension, chronic respiratory diseases, cancer, and metabolic disorders were also reported frequent comorbidity, common in older subjects. However, no certain risk factors have been defined still now.

On the other hand, children seem to be protected thanks to some probable mechanisms. Children usually have fewer comorbidity, ACE2 is underexpressed, and they do not smoke (smoking is associated with increased expression of ACE2), have a large thymic repertoire and sustained innate immunity and more T- and B-regulatory lymphocytes than adults, and received an extensive vaccination program. As a result, children could have a more protective immune response than adults.