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SUPPORTING INFORMATION

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

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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/coronavirus/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 of 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.

TABLE 1 Demographic data and clinical characteristics of COVID+ pediatric patients (data updated on April 16)

	South Lombardy area	Liguria area	Total
Total population	765 000	1 550 000	2 315 000
Pediatric population, <18 y, n (% total population)	120 000 (15.6%)	216 000 (13.9%)	336 000 (14.5%)
Allergic patients <18 y, n (% total population)	37 200 (31%)	71 000 (33%)	108 200 (32.2%)
Asthmatic patients <18 y, n (% total population)	13 200 (11%)	26 000 (12%)	39 200 (11.6%)
Blood eosinophils (cells/μL)[b]	424.6 ± 318.6	446.6 ± 355.4	435.8 ± 336.5
Blood eosinophils (%)[b]	5.57	5.73	5.65
COVID+ total (% total population)	6016 (0.78%)	6039 (0.39%)	12 055 (0.52%)
COVID+ pediatric (% COVID+ total)	18 (0.29%)	22 (0.36%)	40 (0.33%)
Pediatric COVID+			
Gender: male, n/N (%)	10/18 (55.5%)	9/22 (41%)	19/40 (47.5%)
Age (years)[a]	6.4 [0.2-16.0]	5 [1-13]	5 [1-12.5]
Anosmia/dysgeusia[c]	0/11	3/13 (23%)	3/24 (12.5%)
Fever	9 (50%)	18 (82%)	27 (67.5%)
Dyspnea	0	0	0
Cough	7 (38.9%)	15 (68.2%)	22 (55%)
Nasopharyngeal complaints	1 (5.5%)	10 (45.4%)	11 (27.5%)
Gastrointestinal symptoms (vomit, diarrhea)	1 (5.5%)	6 (27.2%)	7 (17.5%)
Asymptomatic	5 (27.8%)	3 (13.6%)	8 (20%)
Radiologically diagnosed pneumonia	3 (16.7%)	1 (4.5%)	4 (10%)
Indication for CT scan	1 (5.5%)	3 (13.6%)	4 (10%)
Hospitalization	13 (72.2%)	11 (50%)	24 (60%)
Blood eosinophils (cells/μL)[d]	153.3 ± 206.6	98.8 ± 78.4	135.2 ± 174.6
Blood eosinophils (%)[d]	1.67	1.64	1.66
Oxygen therapy required	1 (5.5%)	0/22	1 (2.5%)
ICU admission	1 (5.5%)	0/22	1 (2.5%)
Allergy	1 (5.5%)	1 (4.5%)	2 (5%)
Asthma	0	1 (4.5%)	1 (2.5%)

Note: Figures in round parentheses represent percentages.

Abbreviation: n.a.: not available.

[a]Figures represent median values, and figures in squared parentheses represent 1st and 3rd quartiles.

[b]Data concerning 120 allergic children (71 male, median age 9.5 years);

[c]Anosmia/dysgeusia was assessable only in patients ≥3 y;

[d]Comparison between allergic children and COVID-19 children, $P < .0001$ (Mann-Whitney test).

On the other hand, allergy has been rare comorbidity in Chinese COVID-19 patients.[3,4] Very recently, it has been reported that eosinopenia was very frequent (81.2%) in patients deceased for COVID-19,[5] so eosinopenia was considered as a biomarker of poor prognosis. Very recently, eosinopenia was considered the best predictor to facilitate triage of COVID-19 patients.[6] It has been speculated that the reduced eosinophil count was not related to corticosteroid use but related to CD8 T-cell depletion and eosinophil consumption caused by SARS-CoV-2. As ECP and EDN, eosinophil-derived enzymes, can neutralize the virus, the eosinopenia could explain a higher SARS-CoV-2 load that, in turn, overconsumes eosinophils. Eosinophils orchestrate the immune response to a respiratory virus, releasing cytotoxic proteins, increasing NO, producing type 1–associated cytokines, mainly IL-12 and IFN-γ, and recruiting CD8 T lymphocytes.[7] Eosinophils clear viral load, thus guarantying recovery from viral infections. As a consequence, it may be hypothesized that allergic

patients, having eosinophilia, are less affected by COVID-19. The literature data could support this theory.[5-7] Consistently, we found only two allergic children (food allergy and allergic rhinitis) and one child with asthma. We considered peripheral eosinophils (as absolute and relative) and found low counts (Table 1). We compared these COVID-19 children with a large group (120) of allergic children. Allergic children had a significantly higher ($P < .0001$) eosinophil count than COVID-19 patients. Even five (12.5%) COVID-19 children have no (0) eosinophil. Notably, one required admission at the intensive care unit.

To further support the hypothesis that allergy might be "protective," a very recent study provided evidence that allergic sensitization was inversely related to ACE2 expression, and allergen natural exposure and challenge significantly reduced ACE2 expression.[8] These preliminary data need a confirmation that should be provided by more substantial clinical records. However, it has been recently commented that chronic respiratory diseases, including COPD and asthma, seem to be underrepresented in the comorbidities of COVID-19 patients.[9] Therapies could play a possible "protective" effect for respiratory disorders, such as corticosteroids that could contrast viral replication, even though this hypothesis needs confirmation.

The current study has some limitations. The data were derived from the official dataset, but these numbers very probably underestimate the real number of infected people, including asymptomatic subjects. Preliminary unofficial data report a 10% prevalence of positive subjects in the general population, whereas the current prevalence of diagnosed COVID-19 is less than 1%. Moreover, the real prevalence of allergic and asthmatic patients with COVID-19 could be higher if a larger sample were evaluated. Also, the allergic disease prevalence depends on age: The present data concerned young children (median age 5 years). There was also the likelihood that some data on allergy would be missed. Therefore, further study should be performed to confirm this preliminary experience.

On the other hand, children and adolescents with allergy and asthma should be adequately managed during this COVID-19 pandemic, also considering the restrictive rules released by governmental authorities that impose a strict limitation on movements. Therefore, it is essential to implement a series of strategies to manage allergic and asthmatic children and adolescents. As reported by the CDC, children, adolescents, and patients with chronic diseases should strictly follow the fundamental measures of disease prevention:

Clean hands using soap and water or alcohol-based hand sanitizer
Avoid sick people
Clean and disinfect high-touch surfaces in shared household areas, including toys.

Moreover, families should limit social interactions and time with older adults and people with chronic medical conditions, practice social distancing, and avoid travel plans. Also, the CDC highlights that if children meet friends outside of school, they can put every family member at risk of infection. Parents should also encourage playful and scholar activities at home and monitor any signs and symptoms of COVID-19. Besides, in patients with moderate-severe asthma, the CDC recommends explicitly staying at home during the COVID-19 outbreak and strictly following the asthma action plan, taking asthma medications exactly as prescribed.

Inhaled corticosteroids are the cornerstone of asthma therapy both in children and adolescents both in adults. In particular, a 3- to 5-day oral corticosteroid course is the pivotal treatment for asthma exacerbation. As recently reported by the consensus document of the American Academy of Allergy, Asthma, and Immunology (AAAAI), the optimal control of asthma symptoms is the first defense against COVID-19. Considering the lack of evidence, we firmly believe that during the COVID-19 outbreak, all children and adolescents with asthma should stay on their asthma plan. Mainly, children and adolescents with noncontrolled asthma or moderate-severe asthmatic symptoms or on biological therapy should not suspend their asthma medications, including corticosteroids, and follow the therapeutic indications of their healthcare provider. Asthma exacerbations may require emergency care, thus exposing asthmatic children and adolescents to possible sources of SARS-CoV-2.

Moreover, an optimal asthma control should be pursued as a protracted homestay is associated with increased exposure to perennial allergens, including house dust mites, pets, and molds, and indoor pollutants that amplify type 2 inflammation. Also, lack of beneficial physical activity, inactivity, overconsumption of snacks, and cigarette smoking may promote asthma worsening. The counseling represents another critical issue as asthmatic children and adolescents and their parents frequently have emotional disorders that significantly affect asthma and inevitably worsen during this outbreak.

During this viral outbreak, the use of nebulizer may be discouraged unless essential, because the nebulized therapy may allow to aerosolize SARS-CoV-2 and increase the risk of infection, as recently recommended.[10] Therefore, pediatricians and allergists should always encourage the use of the spacer to administer the controller therapy correctly. Data indicating a potential impairment of the immune response to SARS-CoV-2 in asthmatic patients treated with biological therapies are not reported. According to the recent AAAAI consensus, we suggest continuing the administration of allergen-specific immunotherapy and biological agents during the COVID-19 pandemic, unless the child acquires the SARS-CoV-2 infection.

In summary, the rapid spread of SARS-CoV-2 infection and the lack of specific antiviral therapies and vaccines currently require additional medical efforts to prevent COVID-19 and mostly protect patients with chronic diseases. In conclusion, an efficient social distancing of families with asthmatic children remains the best option to prevent COVID-19. Moreover, the use of masks could also be useful to reduce exposure to pollens.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Clinical characteristics of COVID-19 patients combined with allergy

To the Editor,

Coronavirus disease 2019 (COVID-19) is a highly contagious disease that could affect not only the lung but also many other systems and has already infected over 2 471 000 and with more than 169 000 deaths worldwide.[1] Large numbers of clinical studies so far have shown that changes in inflammatory factors and cellular immune function of COVID-19 patients may lead to impaired immune function with an unknown specific mechanism. Allergy is an immune response to antigen stimulation, inducing the release and production of various inflammatory mediators which cause allergic symptoms of different organs, such as allergic rhinitis, bronchial asthma, allergic gastrointestinal disorders, and drug allergy. Whether there is specificity in the evolvement of COVID-19 in allergic patients remains to be explored.

Accordingly, we obtained the medical records and compiled data for 110 patients with laboratory-confirmed COVID-19, between February 1, 2020, and March 8, 2020, in Renmin Hospital of Wuhan University, eliminating those who had uncomplete clinical information or SARS-CoV-2 nucleic acid (nasopharyngeal swabs) test still representing positive. We eliminated 45 patients with underlying disease or operation history among which 3 patients were combined with allergic disease history and were all with drug allergy. Thus, 65 patients were included in our study: 21 patients with combined allergy history (7 males and 14 females; aged from 41 to 88; including 15 patients with a history of drug allergy, 2 patients with asthma, 1 patient with allergic rhinitis, 1 patient with asthma combined with drug allergy, 1 patient with allergic rhinitis combined with drug allergy, and 1 patient with food allergy) were screened out as observation group and 44 patients without combined allergy history were screened out as control group (23 males and 21 females; aged from 30 to 81). We designed a single-center retrospective review, and all the enrolled patients met the criteria of the Chinese Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 7th Edition).[2]

Wendan and Ziang contributed equally to this work.