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Managing childhood allergies and immunodeficiencies during respiratory virus epidemics – the 2020 COVID-19 pandemic

A statement from the EAACI-Section on Pediatrics

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Managing childhood allergies and immunodeficiencies during respiratory virus epidemics – the 2020 COVID-19 pandemic

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Abstract

While the world is facing an unprecedented pandemic with COVID-19, patients with chronic diseases need special attention and if warranted adaptation of their regular treatment plan. In children, allergy and asthma are among the most prevalent non-communicable chronic diseases, and health care providers taking care of these patients need guidance. At the current stage of knowledge, children have less severe symptoms of COVID-19, and severe asthma and immunodeficiency are classified as risk factors. In addition, there is no evidence that currently available asthma and allergy treatments, including antihistamines, corticosteroids, bronchodilators increase the risk of severe disease from COVID-19. Most countries affected by COVID-19 have opted for nationwide confinement, which means that communication with the primary clinician is often performed by telemedicine. Optimal disease control of allergic, asthmatic and immunodeficient children should be sought according to usual treatment guidelines. This statement of the EAACI Section on Pediatrics puts forward six recommendations for the management of childhood allergies and immunodeficiencies based on six underlying facts and existing evidence.

Keywords: COVID-19, SARS-CoV-2, children, allergy, asthma, treatment, corticosteroids, biologics, coronavirus, immunodeficiency.

Introduction

Viruses interact with most living organisms, mostly in a symbiotic way. Nevertheless, this equilibrium can be disturbed in many occasions and lead to outbreaks of disease. In the case of the delicate interaction between viruses and human beings, many significant epidemic outbreaks of viral disease are linked to respiratory symptoms. Humans have been faced in the last 100 years with major pandemics involving viruses. In 1918, the so-called Spanish flu led to more deaths than the civil deaths of the first and second world wars combined. More recently, the H1N1 flu, the severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) led to epidemics to different extents. Currently, the world is faced again with a major pandemic due to a novel coronavirus, the SARS-COV-2 leading to COVID-19 (CoronaVIrus Disease 2019) disease. Epidemiologic data suggest emergence of the virus from an animal market in the city of Wuhan, China, most probably during the last months of 2019 (1). Thereafter, the virus has spread throughout the Asia/Pacific area, to the Middle East, the West and throughout the world (2). At the time of this writing (10th April 2020) the major centers of dissemination are in Europe and North America, although data from other countries may be underrepresented due to lack of testing. Disruptions of social and economic life are significant and by no means comparable to previous respiratory virus pandemics.

What is different in children?

While all humans are at risk of being infected regardless of age, gender or health, vulnerable populations at higher risk of developing a severe form of COVID-19 disease have been identified. Among them, older age is a major risk factor. Since the beginning of the pandemic, it has become rapidly apparent that children less often present symptoms and that these are less often severe. The only systematic review bringing together data on children has been published recently and concluded that children account for 1-6% of the diagnosed COVID-19 cases, often have milder disease than adults and mortality rates are extremely low (3). However, with hundreds of papers published on COVID-19 in the past few months, the problem of reporting the same patients in different manuscripts was raised (4); duplicate reporting may lead to inaccurate scientific record and thus potentially misleading

results in any systematic review and meta-analysis. The first reliable data came from more than 72.000 case-reports reviewed by the Chinese Center for Disease Control and Prevention showing that less than 1% of cases were younger than 10 years of age (5). Another recent report described in detail the clinical characteristics of 171 children treated for COVID-19 at the reference children's hospital in Wuhan (6). The most common clinical signs included cough and pharyngeal erythema. Fever was only observed in 41.5% of the children. Interestingly, although 111/171 (64.9%) were diagnosed with pneumonia, 12 patients had radiologic signs of pneumonia without any symptoms of infection. In the whole cohort, only 3 patients required hospitalization in an intensive care unit for invasive mechanical ventilation. All 3 patients had a preexisting medical condition (hydronephrosis, leukemia or intussusception), one of them, a 10-month-old infant with intussusception had multi-organ failure and died four weeks after admission to the hospital. Asthma and allergies were not mentioned in this case series. In another report, among children aged 1-7 years who were admitted to the hospital in Wuhan, all children including four with radiological evidence of pneumonia and one admitted to the intensive care unit, have recovered (7).

A recent study that covered nationwide case series of 2143 pediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention from January 16 to February 8, 2020, provided important information regarding the epidomiology and transmission patterns of the disease in children (8). In this study, there were 731 laboratory-confirmed cases (34.1%) and 1412 suspected cases (65.9%). Ninety-four (4.4 %) patients were asymptomatic; 1091 (50.9 %) had mild and 831 (38.8 %) had moderate disease which, as a group of non-severe cases (i.e. with no hypoxaemia or organ failure), accounted for 94.1 % of all cases. The proportion of severe and critical cases (n= 125, 5.8%) in each age groups was as follows: within the < 1 year age group 40 of the 379 patients (10.6 %) had severe or critical disease; in the 1-5 year group 36 of the 493 patients (7.3%); 6-10 year age group 22 of 521 patients (4.2%); 11-15 year age group 17 of 413 patients (4.1%) and in the ≥ 16 year age group 10 of 335 patients (3%) had severe disease. There was one fatality of a 14-year-old boy. The data suggested that younger age, especially infants, was represented at a higher proportion among children with severe disease. However, as discussed in the paper and outlined in an accompanying editorial one

should bear in mind that in this study testing for other viruses was not standardized, and two-thirds of cases were clinically diagnosed, but not virologically confirmed (9). In addition, more of the severe and critical cases were in the suspected than the confirmed group which suggests that some suspected cases might be caused by other respiratory infections.

The CDC in the USA recently published a review of laboratory confirmed COVID-19 in children between February 12–April 2 2020 (10). Among 149,082 (99.6%) reported cases for which age was known, 2,572 (1.7%) were among children aged <18 years. The majority of pediatric cases (57%) were male, and male predominance persisted even in infants. Among 345 pediatric cases with information on underlying conditions, 23% (n=80) had at least one underlying condition; most commonly chronic lung disease (including asthma) (n=40), followed by cardiovascular disease (n=25), and immunosuppression (n=10). Information on hospitalization status for children was available for only 745 (29%) cases. Infants accounted for the highest percentage of hospitalisations; of the 95 infants with known hospitalization status, 62% (n=59) were hospitalized, including five who were admitted to intensive care. There was little variation in the percentage hospitalised amongst children >1 year of age. Limitations of this study included substantial missing data, thus statistical comparisons were not possible and need to be interpreted with caution. However, similarly to the Wuhan review of pediatric cases, children were less severely affected than adults, and infants were more likely to be hospitalized. Of note, given the higher percentage of asymptomatic children in the population, the real percentage of pediatric subjects with severe or critical disease may be even lower,.

The reason for the relatively milder clinical presentation in children is mostly unknown. As outlined in the Chinese study several factors in relation to the exposure and host factors may account for this observation; in addition, since the children's immune system is still developing it may react to pathogens differently than do adults (11). Angiotensin Converting Enzyme II (ACE-2) which acts as the receptor for coronaviruses may be structurally and functionally less mature in the airways of children (12–14). As children attend daycare/schools, they are exposed to a variety of viruses including other types of coronaviruses, they may be better equipped with general antiviral defense mechanisms of the immune system. Another potential hypothesis (14) suggested that the simultaneous presence of other viruses in the

respiratory tract mucosa, which is very typical for young children, may limit the growth of SARS-CoV2 by direct virus-to-virus interactions and competition (15). Similar to the observation made in children with SARS (16), the children with COVID-19 infection may not be mounting a generalized cytokine storm but rather may be responding with elevation of specific cytokines. In a recent study with clusters of adults with pneumonia cases in Wuhan, China, the cytokine profile associated with COVID-19 disease severity, was characterised by increased interleukin (IL)-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α (11). It is also possible that children have less severe disease because they have fewer chronic health conditions. It is important to note that although children have less severe COVID-19 disease they are still able to pass on the virus, even whilst asymptomatic (17).

Other factors including asthma and allergic diseases

In addition to age, chronic health conditions such as renal failure, diabetes, hypertension and heart disease are major risk factors for developing more severe symptoms of COVID-19 (18). Patients with asthma (particularly severe or uncontrolled asthma) and immunodeficiency have also been classified to be at increased risk of developing more severe COVID-19, based more on common sense rather than mounting evidence (19). However, recently, the CDC in the US released a Morbidity and Mortality report which suggested that adults with a history of asthma were more likely to be hospitalised with COVID-19; those hospitalised with COVID-19 had a higher rate of a history of asthma (27.3%) than the general population (10%) (20).

While public policy is majorly focusing on ‘flattening the curve’ i.e. preventing a too rapid spread of COVID-19 and on providing adequate healthcare for patients with severe respiratory symptoms in this very aggressive disease, many health providers are faced with questions about safe management of their patients with chronic health conditions. Many elective face-to-face hospital services have been discontinued, in favor of remote consultations that have also been substantially scaled back, which provides its own challenges. The care of children with allergies or immune conditions is being adapted to the current situation, with more remote working and providing

guidance to children to reduce likelihood of infection in children who would be deemed at higher risk of severe COVID-19 disease.

Guidance is strongly needed on how to manage children with allergic diseases during the pandemic; particularly, as the pandemic is hitting the Northern hemisphere during the tree and grass pollen pollination season. How to run a clinic under the condition of the COVID-19 pandemic is reviewed in the EAACI position paper (21). Although, the current COVID-19 pandemic may fade away and hopefully eventually a vaccine may be available, it is unavoidable that new respiratory viruses will appear and that similar questions will arise again in the future. Hopefully these recommendations will be helpful also in future similar events.

Areas of concern and current knowledge

Identifying risk groups

It became rapidly evident that severe COVID-19 infections were particularly prevalent in specific risk groups. A retrospective cohort involving 191 adults hospitalized in Wuhan at the early onset of the disease identified pre-existing comorbidities in 48% of the patients (18). Hypertension was most common followed by diabetes, and by coronary heart disease. Chronic obstructive lung disease was a pre-existing condition in only 6 patients with 4 of them having a fatal outcome due to COVID-19. Asthma or allergy was not mentioned as a risk factor in this population. Older age was associated with increased odds of in-hospital death; this observation has now been confirmed during the course of the disease in Europe and North America.

COVID-19 and allergies

Evaluating asthma and allergy more specifically as potential risk factors, a retrospective study based on electronic medical records from 140 hospitalized COVID-19 adult patients investigated pre-existing asthma or allergic diseases (22). In this adult population, drug hypersensitivity was self-reported in 11.4% and urticaria in 1.4%. However, asthma or other allergic diseases were not reported by any of the patients. Even though there are no data specifically addressing this question CDC states that people of all ages with chronic lung disease including moderate to severe

asthma are listed as having high risk (19). Preexisting allergies have not been classified as risk a factor.

Do allergy treatments increase the susceptibility or severity of CovidCOVID-19 or other viral infections?

Concerns have also been raised regarding a more severe course of COVID-19 in patients already treated with systemic steroids, as patients on oral corticosteroids could have modified immune response predisposing to an increased susceptibility or a higher rate of infection. Unfortunately, direct evidence is lacking. However, various observations provide some indirect evidence. An analysis of previously published studies shows no benefit from adding systemic corticosteroids during the acute phase of COVID-19 infection; in fact this was associated with increased harm due to complications (psychosis, diabetes, avascular necrosis) and delayed clearance of the virus (23). On the basis of this, the WHO has discouraged the use of systemic corticosteroids (24). Lung infections due to RSV are common during infancy and systemic steroid treatment does not either improve, or alter the course of the disease (25). From these studies, it would be presumed that systemic corticosteroids are not helpful in the treatment of every patient with COVID-19. However, some emerging data on the benefits of high doses of systemic corticosteroids in adult patients suffering from acute respiratory distress syndrome (26), along with evidence of the cytokine storm occurring in the later phase of the disease in the most severe cases, has triggered the use of this approach in selected candidates in the context of COVID (27), although the risk/benefit ratio is still unclear (11).

The Global Initiative for Asthma (GINA) (28) and the British Thoracic Society (BTS) (29) do not recommend stopping oral steroids in the management of asthma if the individual is already taking these medications and do not recommend avoiding oral steroids for an acute asthma attack, even if it is due to COVID-19.

There are no data regarding whether the treatment with inhaled corticosteroids (ICS) modifies the susceptibility to or severity of COVID-19. Previous studies have shown that ICS especially when used at high doses, may be associated with an increased risk of pneumonia in adult patients with chronic obstructive pulmonary disease. In this

regard, one should keep in mind that children have different phenotypes of asthma than adults. In children, however, a recent meta analysis has shown that regular use of ICS may not increase the risk of pneumonia or other respiratory infections in children with asthma (30). Early childhood is a time associated with frequent infections due to common respiratory viruses such as respiratory syncytial virus (RSV) or rhinovirus. In children with increased bronchial hyperactivity, recurrent viral infections predispose to episodes of bronchoconstriction. In order to prevent this, these patients are frequently treated with ICS. During such treatments, increased severity or frequency of viral infection have not been observed (31).

Since asthma itself may be a risk factor for the severity of COVID-19 disease and since the use of ICS does not pose an increased risk for pulmonary or systemic infections in children with asthma, their regular use is unlikely to increase the risk of acquiring the infection or increasing the severity of the present infection.

Other commonly prescribed allergy medicines such as antihistamines, bronchodilators or leukotriene receptor antagonists were not reported as risk factors in any studies on SARS-CoV virus infections, and should not be considered as increasing the risk of COVID-19.

Biologics have now become treatment standards in many patients with the more severe forms of asthma or allergies. Again, no patients in the large Chinese series were reported to have being administered by biologics prior to COVID-19. For treatment of severe allergic diseases with biologicals, a recent EAACI expert opinion article suggested continuation in otherwise healthy patients, while during COVID-19 pandemic. Nevertheless, biologics should be paused until recovery in SARS-CoV-2 positive patients (32).

Patients with immunodeficiencies

Since primary immunodeficiencies (PID) are congenital disorders, patients with PID might represent a potential group-at-risk in the current pandemic of COVID-19. From the very onset of the pandemic, a special focus was given to this patient group predisposed to infections with respiratory viruses. An international consensus recently summarized how to best manage patients with PID during the pandemic (33).

According to current knowledge in April 2020, it is not yet known whether any specific form of immunodeficiency poses a particular threat to patients. As a joint project, questionnaires were launched by the Joint Forces of International Societies for Immunodeficiencies to map and follow-up the situation among patients with immunodeficiencies (34). So far, only individual patients (15 patients in total as of April 6, 2020) with immunodeficiency and COVID-19 are listed in the survey. Most of them present a milder course of the disease. Those with a more severe disease course additionally have co-morbidities or complications of their immunodeficiency. As COVID-19 might also trigger complications of an underlying disease, patients with immunodeficiencies should be very carefully followed-up during COVID-19.

The current COVID-19 pandemic might also pose a risk to pediatric patients with secondary immunodeficiencies, such as patients on immunosuppressive therapy for autoimmune or severe allergic diseases. It is recommended to continue the treatment, including immunosuppressants. In the case a secondary deficiency is treated by immunoglobulin substitution, continuation is recommended. The use of convalescent plasma might be considered in these cases in the future, when this now emerging COVID-19 treatment option is scientifically established (35).

Precautionary recommendations for patients with immunodeficiencies follow the national guidelines for the general population and include strict hygiene and social distancing measures to limit exposure. A general consensus has been reached to continue established therapies for the immune disorder, even immunosuppressive therapy for autoimmune complications of the underlying disease (36). However, the current pandemic poses an exceptional challenge and safety concern for patients treated with cellular therapies, not only limited to the field of PID (37).

The main drawback to define tailored safety recommendations for patients with immunodeficiencies arises from our lack of knowledge regarding immune mechanisms during COVID-19. Cytotoxic lymphocytes, essential to control viral infections, were described to be markedly decreased in total cell numbers and NK and CD8+ T cell function was exhausted in patients with COVID-19 infection (38). Moreover, Toll-like receptor 7 activation associated with alpha-interferon and TNF-alpha as well as IL-12 and IL-6 production seem to play an essential role in the control of the viral infection (39).

To increase our knowledge in disease mechanisms, we need to learn from clinical and immunological characteristics of patients with severe in contrast to moderate disease (40). In children and young adults COVID-19 mainly occurs mildly and without life-threatening complications. If COVID-19 causes severe to lethal disease as observed in sporadic cases in these age groups without other co-morbidities, it is tempting to speculate that severity is due to a defect in defence against the infection. Therefore, a targeted search for possible monogenic immunodeficiencies by next generation sequencing and further advanced methods was launched in these patients (41), which will greatly advance our understanding of immune protection against COVID-19.

Recommendations for the management of patients with allergies and immunodeficiencies during the COVID-19 pandemic

Fact 1: Children are at lower risk for COVID-19 infection and have a less severe course of the disease.

Recommendation 1: Fortunately, pediatric allergists are dealing with a patient population that is at low risk for COVID-19. Nevertheless, due to the extent of the disease, severe cases of COVID-19 will also be seen in allergic children, independent of their atopic predisposition and their young age. Pediatric allergists should seek to gain the best control of current allergic symptoms and instruct patients on current recommendations for hygiene and social distancing to reduce the risk of COVID-19 infection. Given the increased stress levels during the COVID-19 pandemic, guidance and support is important for patients and their parents (42).

Fact 2: Whenever possible, diminish or remove risk factors.

Recommendation 2: Uncontrolled asthma is classified as a risk factor, thus asthma control with appropriate medications should be a major goal in such patients. Although asthma is most often multi-factorial, allergies may play a significant role in the pathogenesis of their disease. In particular, during months when seasonal allergies become common, asthma control according to current guidelines should be

undertaken. Pediatric allergists should aim for optimal asthma control. In some countries shielding (home isolation for up to 12 weeks) is recommended for patients with severe asthma (43) but this method cannot be universally applied and each case should be approached on individual basis.

Fact 3: Initial symptoms of seasonal allergy might be misleading as they might resemble those seen in a mild flu-like infection.

Recommendation 3: Seasonal allergy symptoms, especially at the beginning of the season, may resemble flu or common cold and thus may also be suggestive of COVID -19. Pediatric allergists must be aware of this and not be over-suspicious of and yet should not miss COVID-19 in allergic patients.

Fact 4: Treat your allergic patients according to usual guidelines.

Recommendation 4: There has been no scientific evidence that allergy treatments either increase susceptibility to SARS-CoV-2 or the severity of COVID-19 disease. Pediatric allergists should treat patients with allergic asthma, allergic rhinitis or other allergy conditions according to usual guidelines (24), without restricting the use of any specific medication. One exception to this is the advice to withhold biologics during acute COVID19 disease. In addition, there is also reason to believe that proper treatment of these diseases might prevent unnecessary visits to physicians and hospitals and thus reduce the risk of being exposed to the SARS-COV-2 virus. Of note, the Global Initiative For Asthma (GINA) recommends avoiding the use of nebulisers for asthma attacks due to the increased risk of disseminating COVID-19 (to other patients and to physicians, nurses and other personnel), thus pressurized metered dose inhaler (pMDI) via a spacer is the preferred treatment during severe attacks (28).

Fact 5: Current knowledge might evolve and guidelines might change.

Recommendation 5: As the COVID-19 pandemic spreads over the world, increasing number of patients are affected, also including children with allergic diseases. Our knowledge will increase over time, although we do not expect any increasing risk in children with allergic conditions, current recommendations might change according to new findings. Allergists should be flexible and open to the progress of science, as current recommendations might be revised accordingly.

Fact 6: Patients with immunodeficiency have an increased risk for infections with respiratory viruses

Recommendation 6. Representing a potential at-risk-group, patients with immunodeficiency are recommended to strictly follow national precaution recommendations to reduce the risk of infection. To avoid disease exacerbations, patients should stay on their regular medication for their underlying disease as well as its complications, including autoimmune, allergic and other symptoms. Patients with suspected COVID-19 infections should be in close contact with their attending physician and resolve any clinical symptoms immediately. Given the risk of face-to-face consultation, reduced staffing (due to sickness or redeployment), this contact is now often being performed via telemedicine (21,45). Clinical immunologists should follow scientific advances in mechanistic knowledge of COVID-19, which might enable them to define patient tailored safety and treatment recommendations in the future.

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