

EDITORIAL



What are the considerations for treating pediatric asthma during the COVID-19 pandemic?

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel infectious respiratory disease caused by SARS-CoV-2, a coronavirus first identified at the end of 2019 in patients from Wuhan, China. More than 78 million COVID-19 cases and 1,7 million deaths have been unfortunately reported globally since the beginning of the pandemic to late December 2020. Based on currently available data, children appear to be affected less commonly than adults [1]. Although severe cases have been reported, symptoms appear to be milder in children than in adults.

COVID-19 predominantly affects the lungs, and thus it is critically important to assess whether asthma, or other chronic lung diseases, place children at higher risk.

The Centers for Disease Control and Prevention have reported moderate-to-severe asthma as an underlying medical condition at increased risk for severe COVID-19 in adults [2]. It is important to note that there are still conflicting data on asthma prevalence in COVID-19 patients. Although in preliminary studies from China and other countries asthma was underreported, in recent cohort studies the prevalence of asthma in adult patients with COVID-19 in the United States (US) ranged from 7.4% to 17% [3,4]; interestingly, asthma and the use of inhaled corticosteroids (ICS) were not associated with an increased risk of hospitalization in a US cohort of 1526 patients with COVID-19 [5]. Conversely, asthma and severe asthma were associated with COVID-19 mortality in an extensive analysis of United Kingdom patients' electronic health records [6].

To date, few studies reported asthma as a potential risk factor for COVID-19 in children [7,8]. Underlying respiratory conditions, including asthma and chronic lung disease, have also been recently reported in pediatric patients with multi-system inflammatory syndrome in children (MIS-C), a newly recognized syndrome related to SARS-CoV-2 infection characterized by hyperinflammation and multiorgan involvement, presenting with clinical features similar to Kawasaki disease and toxic shock syndrome [9,10]. The pathophysiology of MIS-C is not well understood, and its link with certain underlying medical conditions (including asthma) remains to be further elucidated.

Although very limited information is still available about the impact of asthma and whether it may increase the risk of severe illness from COVID-19 in children, some preliminary considerations may be drawn from the results of recent research conducted in children with asthma.

Angiotensin-converting enzyme 2 (ACE-2) is the host cell receptor responsible for mediating infection by SARS-CoV-2; in addition to binding ACE2, priming of the viral spike (S) protein by the host serine protease TMPRSS2 is required for cell entry. Recent studies demonstrated that the expression of ACE2 in airway epithelium increases with age and seems to be modulated by the type of airway inflammation in patients with asthma. In particular, a lower ACE2 expression has been reported in children with or without asthma compared to adults and in patients with type 2 asthma rather than in non-type 2 asthma [11–13]. Furthermore, *in vivo* studies have shown a reduced gene expression of both ACE2 and TMPRSS2 in sputum among patients with asthma taking ICS, especially among those on higher doses [14]. These preliminary findings may represent potential mechanisms of reduced COVID-19 prevalence in children and patients with allergy and asthma.

Eosinopenia is emerging as an early prognostic biomarker of severe COVID-19 in adults and children [15]. Our group demonstrated a significantly lower eosinophil count in children with COVID-19 than those with allergy and asthma [16]. Since eosinophilia plays a critical role in allergy and asthma pathogenesis, this evidence is consistent with the hypothesis that asthma or other allergic diseases do not seem to increase the risk for poor outcomes with SARS-CoV-2 infection in children.

In this context, a recent study analyzing a cohort of children with allergic asthma in an area of high exposure to SARS-CoV-2 found that asthmatic children with COVID-19 had a mild course of the infection independently from asthma severity [17]; however, the COVID-19 allergic asthmatic children required more rescue therapy with beta2-agonists and controller treatment than those without COVID-19, suggesting a possible role of SARS-CoV-2 in eliciting asthma exacerbation [17]. Still, there is no clear evidence of the role of SARS-CoV-2

as a trigger for asthma exacerbations, unlike other conventional coronaviruses [18].

It is noteworthy that these findings should not lead pediatricians to underestimate COVID-19 in their patients with asthma. Further investigations are required to determine whether asthma represents a risk factor increasing morbidity and mortality of COVID-19 in the pediatric population.

So, what are the considerations for treating pediatric asthma during the COVID-19 pandemic?

In the initial workup of a child with suspected asthma, symptoms such as coughing, shortness of breath, or difficulty breathing may overlap with COVID-19 manifestations. Pediatricians must be aware of the differences between these two diseases, investigate in the clinical history other clues suggestive for allergy and recognize possible wheezing sounds on physical examination. However, even if these findings are consistent with asthma, pediatricians should screen for COVID-19 all children with a worsening cough or shortness of breath, and adequate personal protective equipment (PPE) should be provided to ensure the safety of health-care workers. Since the beginning of the COVID-19 pandemic, pulmonary function testing (spirometry) has been limited to selected cases only to reduce viral transmission [19]. This limitation may complicate the diagnosis and monitoring of pediatric asthma during COVID-19. In this context, impulse oscillometry (IOS) may represent an alternate reliable test to monitor pulmonary function in children with asthma. Being a tidal breath-based technique, IOS may hold good potential in the current pandemic since the expected aerosol generation is much less than spirometry [20].

International experts on pediatric asthma recommend that children with asthma continue taking their asthma controller medications required to keep their asthma well controlled during this time [21,22]. There are no current data that support step-down or suspending the use of asthma medications, such as ICS or antileukotrienes, in children with asthma. Conversely, this could lead to worsen asthma control and increase the risk of severe exacerbations. Although there has been some debate over the use of ICS during the COVID-19 pandemic, there is general consensus that their regular use is unlikely to increase susceptibility to COVID-19 or harm the course of infection [23]. If possible, the use of nebulizers should be avoided since aerosol nebulization may cause dispersion of SARS-CoV-2 into the surrounding environment and increase the risk of infection. Thus, ICS and/or bronchodilators should be administered through a metered dosed inhaler with the help of a spacer [21]. Biologics should not be reduced or discontinued in patients with severe asthma, except for an acute COVID-19 infection [24,25]. Other recommendations include an up-to-date asthma action plan and a regular check of medication adherence and inhalation technique to maintain good asthma control. In children with mild to moderate or well-controlled asthma, routine follow-up visits may be delayed, and virtual care options, including telehealth, may ensure the continuity of care [26].

Current guidelines recommend prompt treatment with oral corticosteroids (OCS) in moderate to severe asthma exacerbations if patients are poorly responsive to bronchodilators, as indicated by usual guidelines [21]. World Health Organization

(WHO) recommend corticosteroids (namely dexamethasone) for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory support. This recommendation is supported by the results of randomized trials conducted in adults. Although corticosteroids have been associated with decreased mortality in adult patients, trials in children are ongoing and the benefits and risks are uncertain. In contrast, dexamethasone (or other corticosteroids) should not be used for either prevention or treatment of mild to moderate COVID-19 [27]. These concerns on the use of corticosteroids are mainly due to the potential impairment of the protective innate antiviral immune responses. There is currently limited evidence on the optimum management of COVID-19-associated asthma exacerbations. However, the decision to treat a child with an acute exacerbation of asthma with OCS should not be delayed if clinically indicated [21,28]. In rare cases, patients with severe asthma requiring long-term treatment with OCS should be continued in the lowest possible dose to prevent the risk of severe exacerbations [21,28]. In these children, an add-on biologic therapy should also be considered as these medications have a proven steroid-sparing effect.

Future studies should focus on characterizing the immunopathology of COVID-19-related asthma exacerbation in children to determine the optimum approaches to managing these patients.

2. Expert opinion

We concur with expert groups that every effort should be made to avoid exposure to the SARS-CoV-2 virus and all regular medications necessary to maintain asthma control, including ICS, OCS and biologic agents (e.g. omalizumab, mepolizumab, and dupilumab), should be continued in children with asthma during the COVID-19 pandemic.

A great research effort is now aimed at identifying whether biologics may modulate the immune susceptibility to COVID-19 in asthmatic subjects, based on previous clinical and laboratory observations. Children with severe asthma are more susceptible to virus-induced asthma exacerbations, particularly those with higher serum IgE levels. In the PROSE study, anti-IgE treatment (omalizumab) reduced the frequency and duration of rhinovirus infections in children with asthma through enhanced IFN- α responses in plasmacytoid dendritic cells. Whether blocking IgE also decreases susceptibility to other respiratory viral illnesses, including SARS-CoV-2, remains unknown. Another interesting finding has been the association between COVID-19 infection and peripheral blood eosinophil counts. Based on accumulating data, patients with severe COVID-19 show a trend toward persistent eosinopenia, correlated with high disease severity and low recovery rates. As the pathophysiology for eosinopenia in COVID-19 could be multifactorial, whether eosinopenia is the cause or effect of the infection needs further investigation. Clarifying this topic will be of fundamental importance for patients with severe asthma receiving biologics anti IL-5/IL-5R, as they reduce blood eosinophil counts. Also, the effects of type 2 inflammatory cytokines, such as IL-4 and IL-13, on ACE2 and TMPRSS2

expression in the airways should be further investigated, as they are directly targeted by dupilumab.

Unlike adults, there are currently few data on the incidence and the frequency of children with COVID-19 receiving biologics for severe asthma. Further studies are needed to allow any definitive conclusion on the association between severe asthma, biological therapy, and SARS-CoV-2 infection.

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