

R E V I E W

Allergy and COVID-19

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Abstract

The first cases of as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported in Wuhan, China in December 2019. The World Health Organization declared the global pandemic in March 2020. Coronavirus disease 2019 (COVID-19) showed high rates of mortality in the adult population, whereas a mild course was observed in childhood. Allergic diseases, characterized by a type-2 polarization of the immune system, were considered one of the major risk factor of severe COVID-19. Large amounts of clinical data and expert opinions have been collected since the pandemic outbreak. This review summarizes the latest insights on COVID-19 and allergy. (www.actabiomedica.it)

Key words: COVID-19, SARS-CoV-2, allergy, allergic asthma, phenotype, eosinophil, children, adolescents.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic had a significant impact on our society and our health system. The virus infected over million people worldwide, and the number of total deaths is more than 3.9 million (1). Italy was the first European country to be hard hit by the pandemic (2-4). Currently, the development of different vaccines and the presence of hygienic-sanitary measures protocol, individual prophylaxis, and availability of adequate personal protective equipment (PPE) have contributed to the reduction of infections, hospitalizations, and deaths (5, 6). In this setting, children have not been fortunately the face of this pandemic. Although most children with SARS-CoV-2

infection had mild symptoms or were asymptomatic, severe complications have been also described in some children, especially for those with underlying medical conditions (7-10). In the last year, attention was paid to the identification of significant risk factors correlated with the severity of the disease. Allergic disease was considered a risk factor in childhood age due to a reduction in the T-helper 1/T-helper 2 (Th1/Th2) ratio. The Th2 polarization in allergic children is related to eosinophilia, high immunoglobulin E levels, and enhanced IL-4, IL-5, IL-13 cytokines but also to an impaired innate IFN response, which is the first-line defense against viral infection (11-13).

In this paper, we critically review the available literature, focusing on the effect of allergy and asthma on the risk and outcome of COVID-19.

Asthma, allergy, and COVID-19

The first pediatric case of SARS-CoV-2 infection reported in the literature was in January 2020 in a 10-year-old boy from Shenzhen, China, whose family had recently visited the city of Wuhan (14). The available data confirm that COVID-19 is less severe in children than in adults. In the latest and largest study in the UK, which included 20,133 patients hospitalized for COVID-19, 310 patients (1.5%) were less than 18 years old, and 194 (1.0%) were less than five years old. Asthma was reported in 2540/17535 patients (14.5%) (15). Concomitantly, multicenter Italian and Chinese studies showed a very low mortality rate in children and adolescents than adult population (16–19). Italy has registered 27 death <18 years old (20). Several theories have been proposed to explain the reduced severity of SARS-CoV-2 infection in the pediatric population: a lower expression of angiotensin-converting-enzyme 2 (ACE-2) on the airway's epithelium, a more efficient and active innate immune response, and a less intense immunopathological reaction to the infection called “cytokine storm” (21). It has been reported that the virus surface spike glycoprotein binds host ACE-2 as a receptor for entry into cells (22). This receptor seems to be lower expressed in the nasal airway mucosa in pediatric age than in adults, and in the airway epithelial cells of children with allergic sensitization and allergic asthma (23, 24). Another mechanism, suggesting by *in vitro* study with Coronavirus 229E, is related to antiasthmatic drugs. Long-acting beta-2-agonists and inhaled corticosteroids, in fact, may inhibit viral replication and cytokine relapse in COVID-19 infection (25). Kimura et al. demonstrated that ACE-2 expression is strongly downregulated by inflammatory type-2 cytokines such as IL-13 (26). However, none of the major worldwide epidemiological studies, including a pediatric series, have assessed whether asthma or allergic diseases include a risk factor for severe COVID-19.

The pediatric position paper of the European Academy of Allergy and Clinical Immunology (EAACI) suggested that patients with severe or uncontrolled asthma may have a higher risk of developing severe COVID-19. However, there is no clear evidence that patients with asthma are at increased

risk of contracting the disease and developing a poor outcome (27). One of the first Chinese case studies reported a prevalence of asthma corresponding to 0.9% in patients hospitalized for COVID-19, significantly lower than in the general population, which prevalence is 6.4% (28).

Conversely, studies conducted in the United States showed a high rate of asthma in children and adults with COVID-19 than previously reported in China and Europe (29). Using big data analytics and artificial intelligence Izquierdo et al. analyzed a large series of 71,182 patients with asthma founding only 1,006 (1.41%) cases of COVID-19. However, the lower prevalence of asthma among COVID-19 cases could result from methodological biases due to overestimating or underestimating the asthma diagnosis. In addition, there is a high risk of not diagnosing COVID-19 disease, particularly in children; mild disease in this population could be confused with asthma exacerbations (30, 31). A British study analyzed data from a large case series of 17 million adults, including 10,926 deaths due to COVID-19, reporting that asthma was significant comorbidity in SARS-CoV-2 infection and death related (32). However, the pediatric population was not included in this broad analysis. In a South Korean study, the authors suggested using asthmatic phenotype to identify which phenotype has a greater risk of SARS-CoV-2 infection. The authors noted that patients with allergic rhinitis and allergic asthma had lower hospitalization rates, suggesting that allergic disease may have a potential protective effect (33). In an Italian survey (198 children), Tosca et al. reported no significant difference between allergic and non-allergic patients with concern to the hospitalization rate and pneumonia and oxygen therapy prevalence due to COVID-19 (34). A paradoxical phenomenon reported is that asthmatic exacerbation decreases during COVID-19 pandemic, probably due to less exposure to outdoor aeroallergens, reduced pollution with the lockdown, fewer viral triggers due to school pre-school closure (35). In a survey proposed by the Paediatric Assembly of the European Respiratory Society (ERS), only a small minority of SARS-CoV-2-infected children presented with an asthma exacerbation, and only 5 patients were admitted to PICU (36).

The role of eosinophils cells in COVID-19

Several authors have proposed eosinophils cells as a possible prognostic biomarker in patients with severe or critical COVID-19. In a retrospective Italian review in 52 children and adolescents with mild SARS-CoV-2 infection, only two patients were allergic (allergic rhinitis and atopic dermatitis, respectively), and only one was asthmatic. Therefore, it was a small sample of subjects; the percentage of allergy and asthma cases was lower than the general average of the two diseases in the Italian population, or rather about 30% and 10%, respectively. The authors suggested a protective role played by eosinophil cells, higher in allergic disease and type-2 asthma than in healthy children (37, 38). Many studies supporting these data noted absolute eosinophil counts below the normal range in patients admitted with COVID-19. Importantly, eosinopenia resolved after discharge in all surviving patients (39, 40). The pathogenesis of eosinophils decrease in COVID-19 remains unclear. Several mechanisms are described: eosinophil apoptosis induced by type 1 IFN released during the acute infection, decreased eosinophilopoiesis, and reduced expression of chemokine receptors/adhesion factors (41). However, there are still many open questions in the interaction between asthma and SARS-CoV-2 infection.

Asthma control management during the pandemic

An important aspect concerns the use of anti-asthmatic therapies during the pandemic. The GINA International Guidelines recommend that asthmatic patients continue using asthma control medications, including inhaled corticosteroids (ICS) during the COVID-19 outbreak (42). EAACI members suggested continuing biological therapies in patients with severe asthma and initiated in patients who can benefit, according to current clinical practice, in order to limit exacerbations and ensure oral corticosteroids sparing (26). The Italian Pediatric Allergology and Immunology Society (SIAIP) stated that biologics should be discontinued in the case of COVID-19 (43). Moreover, allergic asthma as well as other atopic manifestations do not contraindicate mRNA COVID-19 vaccines (44).

Although absolute eosinopenia is associated with the more severe COVID-19, requiring intensive care, several surveys concluded that therapy useful to reduce type 2 inflammation and eosinophils is safe during the SARS-CoV-2 pandemic. Despite these doubts, some studies have shown that the reduction of eosinophils during treatment with biological drugs does not invalidate the clinical and immunological response to SARS-CoV-2 (45). In this regard, an Italian multicenter observational nationwide survey in children and adolescents treated with biological drugs, such as Omalizumab, Mepolizumab, and Dupilumab, for severe asthma, chronic urticaria, and severe atopic dermatitis was conducted. All biological drugs resulted effective and safe during the pandemic. In particular, out of 308 children and adolescents (mean age 12.8 years, 161 males), only three subjects treated with Omalizumab developed mild symptoms of SARS-CoV-2 infection, while nine subjects treated with Mepolizumab and 13 with Dupilumab developed an asymptomatic form of COVID-19.

Conclusion

Despite the initial hypothesis that allergy and asthma increased the risk for COVID-19 infection, to the best of our knowledge, this is still an open question; the rapid accumulation of collaborative data from around the world will begin to provide. All of the recommendations support continuing the antiasthmatic treatment (particularly ICS, long-acting bronchodilators, anti leukotriene drugs, and, if necessary, oral corticosteroids) to maintain asthma control. Indeed, discontinuation of therapy would increase the risk of severe exacerbations and the need for intensive care. Severe asthma patients should continue therapy with biological drugs and consider administering therapy at home.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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