



# Childhood Asthma and Covid 19

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## ABSTRACT

Coronavirus disease 2019 (Covid 19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS CoV 2) and causes lymphopenia, immunosuppression, inefficient T and B cell immunity, cytokine storm, and destructive tissue inflammation. Since COVID 19 is a multi-system disease predominantly affecting the lungs, there is doubt on whether chronic lung diseases place patients at higher risk and SARS CoV2 leads to asthma exacerbation. None of the studies have reported asthma or recurrent wheezing as a comorbidity or risk factor for Covid 19 in children up to now. Notably, further studies are needed to explore the relationship between Covid 19 and asthma to improve clinical practice and decrease morbidity and mortality.

**Keywords:** Covid 19, SARS CoV 2, asthma, children

Coronavirus disease 2019 (Covid 19) is a pandemic infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and causes lymphopenia, immunosuppression, inefficient T and B cell immunity, cytokine storm, and destructive tissue inflammation (1). The main presenting clinical symptoms are fever, cough, chest tightness/dyspnea, myalgia, fatigue, and gastrointestinal symptoms (nausea, diarrhea, abdominal pain). It may however end up with severe pneumonia, thrombotic complications, multi-organ failure, and death (2, 3).

The first pediatric case was reported in January 2020 in a 10-year-old boy from China, whose family had visited Wuhan (4). The route of transmission to children is by close contact with family members or a history of exposure to the epidemic area (5). Covid 19 creates a lower burden in children than in adults, although all ages are affected (6). There is large proportion of asymptomatic or mildly infected children indicating the difficulty in identifying pediatric patients without clear epidemiological information, leading to an increase in the spread of SARS CoV2 (5). In the United Kingdom, among 20.133 patients hospitalized for Covid 19, only 310 (1.5 %) were under 18 years of age (7). Fatality is also extremely rare in children and adolescents (8).

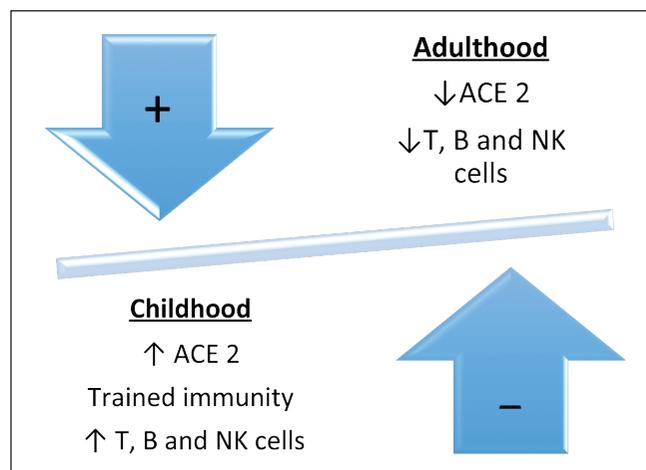
Asthma is characterized by chronic airflow limitation and reversible airway obstruction with inflammation in the lung. The most frequent trigger of asthma exacerbation is viral infections, especially with rhinovirus and respiratory syncytial virus, which often cause upper respiratory tract infections in healthy subjects (9). Seven CoVs are known to cause human disease and these can be divided into non-SARS HCoV (low pathogenic) including 229E, NL63, OC43, and HKU1; and SARS HCoV (high pathogenic) including SARS CoV1, SARS CoV2 and MERS CoV (10). Non-SARS HCoV may be responsible for acute bronchiolitis and acute gastroenteritis in hospitalized children (11). Besides, these viruses trigger asthma attacks both in children and adults (12). Co-morbidities concerning cardiovascular diseases and hypertension, oncologic diseases, immunosuppression and diabetes, and other host-related factors are adverse prognostic factors for Covid 19 (13). Since Covid 19 is a multi-system disease predominantly affecting the lungs, there is doubt whether chronic lung diseases place patients at higher risk and SARS CoV2 leads to asthma exacerbation.

In a study including 2135 pediatric patients with Covid 19 in China, more than 90% of all patients had asymptomatic, mild, or moderate disease; however, nearly half of the children developed pneumonia (14). The

presenting respiratory manifestations in children were mainly dry cough, pharyngeal erythema, tachypnea, and rarely rhinorrhea and nasal congestion (15). The chest radiograph reveals infiltration of the bronchovascular bundles, wide-spread patchy consolidation, and reduction of transparency (16). The CT findings of Covid 19 in pediatric patients are not specific and include ground glass opacity, mainly in the peripheral and posterior lungs with more localized extent, lower attenuation, and less lobular involvement, consolidation and interlobular septal thickening (17). Pediatric data regarding SARS-CoV-2 infection in patients with underlying chronic conditions are limited. Lu et al. have reported 3 children hospitalized in the intensive care unit among 171 PCR-confirmed Covid 19 cases with comorbidities including hydronephrosis, leukemia, and invagination (18). In Spain, 25 children in a cohort of 41 subjects have been hospitalized due to SARS CoV2 and four children have been transferred to the intensive care unit, with one having a history of recurrent wheezing. The diagnosis on admission were bronchiolitis (n=5) and asthma exacerbation (n=1) in some of these patients (19). The CDC Covid 19 Response Team has reported that data were available for 345 pediatric cases on underlying conditions, 80 (23%) had at least one underlying condition, among 2572 pediatric patients (median age was 11 years). The most common underlying conditions were chronic lung disease (including asthma) (n=40), cardiovascular disease (n=25), and immunosuppression (n=10) (20). An international online survey, which was conducted to describe the impact of Covid 19 on pediatric asthma services and the disease burden caused by these patients, included 61 pediatric allergy centers from 27 countries. Suspected cases (n=100) of Covid 19 in children with asthma were reported in only 14% of centers and only 15 patients were confirmed. The most frequent respiratory symptoms were cough (73%), nasal discharge or blockage (60%), wheeze (40%), and breathlessness (40%). Eleven of these children (73%) had mild disease, and 3 (20%) had moderate disease, and only 1 case (6.7%) was hospitalized due to Covid 19 (21).

None of the studies have reported asthma or recurrent wheezing as a comorbidity or risk factor for Covid 19 in children up to now. This was also similar in two adult studies published from China (22, 23). However, the prevalence of asthma was 9% in 5700 patients hospitalized with Covid 19 from all age groups in the New York City area (24). The UK experience showed that 14% of admissions were patients with asthma (7). In Russia, Avdeev et al. demonstrated the prevalence of asthma was 1.8% among 1307 intensive care unit (ICU) patients

with SARS-CoV-2 pneumonia who required mechanical ventilation (25). SARS-CoV-2 enters the cell by the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) and uses a serine protease transmembrane serine protease 2 (TMPRSS2) for S protein priming of the virus (26). Kimura et al. demonstrated that IL-13 exposure reduced ACE2 and increased TMPRSS2 expression in the airway epithelial cells of asthmatic patients. Also, tissues from type 2 cytokine-high allergic patients showed significantly lower expression of ACE2 (27). Inhaled corticosteroids might at least partly prevent the development of severe SARS-CoV-2 infection since inhaled corticosteroids were associated with lower ACE2 or TMPRSS2 gene expression in sputum from asthmatic patients (28, 29). Besides, serum ACE activities in children are reported to be higher and increase progressively from 4 to 13 years of age, and then gradually decrease until reaching the values for adults (30). ACE may be structurally and functionally less mature in the airways of children (31). Children are still exposed to a variety of viruses including other coronaviruses and therefore may have better general antiviral defense mechanisms (31). The age-dependent maturation of the immune response occurs with repeated stimuli and results in enhanced innate function (trained immunity) representing innate immune memory, and it is formed by innate immunity cells that became “memory cells” after antigen exposure (32). In children with Covid 19, peripheral blood lymphocytes remain mostly in the normal range, suggesting less immune dysfunction compared to adults with decreased lymphocyte count and lymphocytopenia. In healthy children, lymphocytes and especially NK cells are higher in amount than in healthy adults (Figure 1) (32).



**Figure 1.** The reasons of the milder disease course of Covid 19 in children compared to adults.

**Table I. ARIA-EAACI statement.**

1. In areas where Covid 19 is prevalent, screening protocols for Covid 19 should be applied to anyone with worsening respiratory symptoms, and personal protective equipment should be used.
2. In areas where Covid 19 is prevalent, lung function testing procedures should be postponed if not deemed absolutely necessary; portable personal devices measuring PEF and FEV1 can be used in the meantime to monitor asthma control using the telemedicine approach.
3. In accordance with the Global Initiative for Asthma (GINA) patients with asthma should not stop their prescribed inhaled corticosteroid controller medication (or prescribed oral corticosteroids). Stopping inhaled corticosteroids may have serious consequences.
4. Long-term oral corticosteroids may sometimes be required to treat severe asthma, and it may be dangerous to stop them suddenly.
5. Oral steroids should continue to be used to treat severe asthma exacerbations.
6. In patients infected by SARS-CoV-2 (symptomatic or asymptomatic), nebulisation (which increases the risk of deposition of virus into the lower airways) should be replaced by spacers of large capacity.
7. In accordance with the NICE in non-SARS-CoV-2 infected patients, we propose
  - To continue biologics because there is no evidence that biological therapies for asthma suppress immunity
  - To consider whether the patient can be trained to self-administer, or could be treated at a community clinic or at home, if the patient usually attends a hospital for biological treatments,
  - To carry out routine monitoring of biological treatment remotely if possible
8. In SARS-CoV-2 infected patients we propose to cease the treatment until resolution of the disease is established, in accordance with the EAACI. Thereafter, the administration of the biological should be re-initiated.

## CONCLUSION

Children are at lower risk for Covid 19 and have a less severe course of the disease (33). However, it would be better not to underestimate Covid 19 in asthmatic children since there are still many unknowns. According to the ARIA-EAACI statement on asthma and Covid 19, patients with asthma should not stop their prescribed inhaled corticosteroid controller medication, and systemic corticosteroids should continue to be used to treat severe asthma exacerbations (Table 1) (34). Notably, further studies are needed to explore the relationship between Covid 19 and asthma to improve clinical practice and decrease morbidity and mortality.

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