



# Role of SARS-CoV-2 in Asthma Exacerbations

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## ABSTRACT

Asthma is one of the most common chronic respiratory diseases in the world and there is great concern about the effect of COVID-19 infection on asthma severity and control. Although the link between asthma and COVID-19 infection remains to be determined, available data indicate that asthma does not seem to be a risk factor for severe COVID-19. This review aims to summarize the updated data about the association between viral infections and asthma exacerbations including COVID infection and management of asthma flare-ups during the COVID pandemic, based on the recommended asthma guidelines.

**Keywords:** Asthma, severe asthma, asthma attack, asthma exacerbations, viral infection, COVID-19, SARS-CoV-2

Asthma is the most common disease in both children and adults, and it is estimated that the number of individuals with asthma will grow by more than 100 million by 2025 (1). Despite development of evidence-based asthma guidelines and appropriate regular therapy, patients with asthma experience exacerbations that may cause disease morbidity, an increase in health care costs, and a decrease in lung function and health quality of life (2). Respiratory viruses are the most common trigger for asthma exacerbations and have been detected by PCR in 85-95% of children with recurrent wheezing or asthma exacerbation, and 80% of adults with asthma exacerbation (3).

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in December 2019 and a total of 15,114,511 cases with more than 619 000 virus deaths have been reported worldwide as of 22<sup>nd</sup> July 2020 (4). The SARS-CoV-2 virus is considered an airborne pathogen (5), so it is possible that the virus may cause asthma flare-ups. Although it is not yet proven that COVID-19 infection is a risk factor for asthma exacerbations, many clinicians have questioned whether acute respiratory infection with SARS-CoV-2 affects the asthma attack risk or attack severity, especially in severe asthma patients. Available data is

limited, and it is difficult to assess the prevalence of asthma attacks due to COVID-19 infection in asthma patients. The Centers for Disease Control and Prevention (CDC) has stated that subjects with moderate to severe asthma may have an increased risk for COVID-19 and the infection may lead to an asthma attack, pneumonia, or acute respiratory disease (6). However, the ARIA-EAACI statement on Asthma and COVID-19 has reported that asthma does not seem to be a risk factor for severe COVID-19 (7). Only asthma patients using oral corticosteroids were defined as a risky group for COVID-19 or severe asthma flare-ups (7). This review aims to summarize the updated data about the association between viral infections and asthma exacerbations including COVID infection and management of asthma flare-ups during the COVID pandemic, based on recommended asthma guidelines.

## Viral Respiratory Infections in Asthma Exacerbations

Viral respiratory infections and viral colonization in the respiratory tract are the main factors associated with childhood-onset asthma (8). Rhinovirus is a non-enveloped positive-strand RNA virus from the family of Picornaviridae, and is classified into three species: RV-A, B, and C (9). Asthma exacerbations and disease severity are closely linked to RV infections. RV has been detected as a main trigger in approximately 90% of pediatric

patients having asthma flare-ups and has been shown to be related with asthma hospitalizations (10). RV subtypes A and C are detected most frequently in hospitalized and intensive care unit (ICU)-hospitalized asthma patients (9,10). RV infections are more common in older children (11). Respiratory syncytial virus (RSV) is a single-stranded enveloped RNA virus with 2 major antigenic groups, A and B, and is from the Paramyxoviridae family (12). RSV-induced bronchiolitis is associated with the development of asthma and RSV is a trigger of wheezing and asthma attacks in infants, young children, and adults (12). While RV is linked to the development of atopic asthma, RSV infection is a risk factor for the development of nonatopic asthma (13).

Asthma exacerbations have also been associated with infection with other respiratory viruses, including adenovirus, bocavirus, cytomegalovirus (CMV), enterovirus, herpes simplex virus (HSV), influenza virus, and coronavirus (14). The mean prevalence of adenovirus, bocavirus, coronavirus, CMV, enterovirus, HSV, influenza virus, metapneumovirus, parainfluenza virus, RV and RSV in adult and pediatric patients having acute asthma attacks was found to be 3.8%, 6.9%, 8.4%, 7.2%, 10.1%, 12.3%, 10.0%, 5.3%, 5.6%, 42.1% and 13.6%, respectively (14). Human bocavirus is a parvovirus and is associated with recurrent wheezing episodes (15). Bocavirus infections are common in young children at the age of 2 to 5 years (9). Although influenza virus infection is frequently seen during asthma attacks in adults, it can be detected in all age groups (9,15). The prevalence of influenza virus infection in patients admitted with an acute asthma attack is about %20 in children and 25% in adults (15). Influenza vaccine is recommended in asthma patients. However, the vaccine has been found not to be significant in reducing the number and the duration of exacerbations in asthma patients (16).

### **Coronaviruses and Asthma Exacerbations**

Coronaviruses are associated with a low rate of asthma exacerbations and can mainly cause upper airway infections (9). A novel coronavirus SARS-CoV-2, like the two other human coronaviruses of SARS-CoV and MERS-CoV, uses angiotensin converting enzyme-2 (ACE2) receptors to enter the human body (17, 18). ACE2 receptors are expressed in the kidneys, testis, brain, and lungs (17). High ACE2 expression has been identified particularly in type II alveolar cells of lungs (17). Therefore, SARS-CoV-2 can easily reach the lower airways by binding to ACE2

receptors in the bronchi cells and type II alveolar cells, and may aggravate asthma. However, the ARIA-EAACI statement has reported that asthma does not seem to be a risk factor for severe COVID-19 (7).

Asthma itself or the use of inhaled steroids seem to have a protective effect against SARS-CoV-2 infection. Peters et al. investigated the differences in ACE2 gene expression in the sputum cells of 330 asthma patients and 79 healthy controls (19). Gene expression of ACE2 was similar in asthmatic and healthy subjects. Interestingly, they showed that the use of inhaled corticosteroids was associated with a lower expression of ACE2 after adjustment for asthma severity (19). Sajuthi et al. used nasal airway transcriptome and network co-expression analysis to identify the cellular and transcriptional factors in COVID-19 infectivity by using a pediatric cohort including 695 subjects with asthma and healthy controls between the ages of 8 and 21 years (20). They also focused on ACE2 expression and found that IL-13 mediated T2 high inflammation had a major role in ACE2 downregulation (20). These study results suggest that SARS-CoV-2 may not cause severe COVID or asthma attacks due to the protective effect of reduced ACE receptors and inhaler steroid use in asthma patients. More clinical studies are warranted to understand the role of SARS-CoV-2 on the severity and the risk of asthma exacerbations.

### **Management of Asthma Attacks During the COVID-19 Pandemic**

GINA recommends continuing asthma medications, including inhaler corticosteroids and oral corticosteroids if prescribed, to prevent asthma attacks (21). Written asthma action plans are needed for all asthma patients to minimize face-to-face contact. Written asthma action plans will help patients to recognize and manage the asthma attacks by themselves. If the patients have symptoms and signs of an asthma exacerbation and it is clinically indicated, a short course of oral corticosteroids can be used (22, 23). Use of nebulizers and spirometry should be avoided in confirmed or suspected COVID patients (21). Aerosols are released from the fluid in the nebulizer chamber during expiration; SARS-CoV-2 is transmitted through droplets and the use of a nebulizer can increase the risk of infection by 0.9 times (24). Unlike other aerosol-generating procedures, a nebulizer may have less infection risk, if it is not contaminated (23). Therefore, the NICE guidelines recommend continuing the use of the patients' own nebulizer at their home (22). However, clinicians

should firstly prefer inhalers, chambers, or spacers instead of nebulizers. If the nebulizer will be used, mesh nebulizers should be preferred over jet nebulizers, and a mouthpiece should be preferred over a face mask (23). Washing hands before and after the use of nebulizer, not sharing the device with the other patients, and cleaning the device according to the manufacturer's instructions are also important steps of the use of a nebulizer during the COVID pandemic (23). Nebulizers can transmit viral droplets for 1 meter (21). Taken together, isolating COVID patients in well-ventilated rooms with open windows and staying at least 1 meter away from the patients during nebulizer use can be effective to minimize the risk of infection. Peak flow meter use should be postponed during the COVID pandemic at the emergency departments. Clinicians should follow the infection control recommendations while using oxygen therapy or invasive/non-invasive mechanical ventilation for severe asthma attacks (21).

## CONCLUSION

In summary, there is no clear evidence that patients with asthma are at a higher risk of an acute asthma attack due to COVID-19 infection. Patients should continue their asthma medications during the COVID pandemic. The recommended asthma guidelines should be followed by clinicians to minimize the COVID infection risk while continuing to properly and effectively treat patients with asthma attacks.

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