



# SARS-CoV-2 infection and COVID-19 in asthmatics: a complex relationship

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Risk of severe coronavirus disease 2019 (COVID-19) after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is increased in patients with certain comorbidities, including chronic obstructive pulmonary disease (COPD). By contrast, epidemiological data from many (but not all) countries indicate a low prevalence of asthma among patients with severe COVID-19. This reduced risk of severe COVID-19 may apply specifically to patients with the type 2 asthma endotype, which is most common in childhood asthma.

It is now well established that several comorbidities comprise an increased risk for infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19) severity or COVID-19-associated mortality. Among them are diabetes, hypertension, metabolic syndrome, obesity and coronary heart disease. Surprisingly, however, patients with chronic inflammatory lung disease, particularly bronchial asthma or chronic obstructive pulmonary disease (COPD), show a more complex association with SARS-CoV-2 infection and COVID-19.

In general, individuals with asthma are more susceptible to respiratory viral infections, and these infections are a major cause for acute and severe asthma exacerbation. For example, individuals with asthma make up more than 20% of patients hospitalized owing to influenza virus infection in the USA<sup>1</sup>, and up to a third of acute asthma exacerbations were attributed to influenza virus infections among adult outpatients with asthma. One would expect, therefore, to see more patients with asthma among those (hospitalized) with COVID-19. However, global epidemiology of patients with asthma and COVID-19 presents a complex picture. Studies from most regions including China, Italy, Spain, Belgium, Israel, Mexico, Brazil, Saudi Arabia and India report a lower prevalence of asthma among patients hospitalized with COVID-19 than in the general population in the respective region<sup>2</sup>. By contrast, a higher prevalence of asthma among patients hospitalized with COVID-19 was reported by studies from the USA, UK, Ireland, Korea and Australia<sup>2</sup>.

Whether asthma is associated with worse COVID-19 outcomes is unclear. A prospective cohort follow-up study conducted in France included 768 patients hospitalized with COVID-19, of which 37 reported a history of asthma, and showed that patients with asthma were not over-represented among those with severe pneumonia

owing to SARS-CoV-2 infection. Similar reports from other countries (including China, USA, Italy, Spain, Switzerland and Saudi Arabia) also found that patients with asthma were not at increased risk for severe COVID-19 (REF.<sup>3</sup>). Conversely, a Korean cohort of 7,340 individuals who tested positive for SARS-CoV-2 revealed that the rate of severe clinical outcomes of COVID-19 was 6.9% in patients with asthma, compared with 4.5% in those without asthma. This study also reported that individuals with non-allergic asthma had a greater risk for severe outcomes of COVID-19 than those with allergic (type 2) asthma. Finally, whether SARS-CoV-2 infection triggers asthma exacerbation, as other respiratory viruses do, is an important question; so far, data indicate that it does not induce severe asthma exacerbation.

Although COVID-19 can affect people of any age, children are generally less affected by severe infections than adults. Multiple international agencies caution that babies less than 1 year of age or children with comorbid diseases, such as asthma, may be at higher risk of severe illness from COVID-19. However, there is a paucity of data to inform us about comorbid risk factors in paediatric patients infected with SARS-CoV-2. In a recent meta-analysis of asthma and COVID-19 risk or severity in children, only five systematic reviews yielded clinical information; none reported asthma or recurrent wheezing as a comorbidity or risk factor for COVID-19 (REF.<sup>3</sup>). Only one study reported asthma as a potential risk factor for severity of, but not mortality from, COVID-19 in children. In conclusion, although the prevalence of asthma is high among children and adolescent populations, there is currently no indication that children with asthma are at higher risk for (severe) COVID-19 than children without asthma; however, the database sample is small and mechanistic studies are lacking.

So what is the relationship between COVID-19 and other chronic inflammatory lung diseases, such as

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COPD? Results from four comprehensive meta-analyses of COVID-19 and COPD have been recently published. A meta-analysis of 12 studies with 2,794 patients with COVID-19, including 596 (21.33%) severe cases, shows that COPD was a risk factor for severe course of COVID-19 (OR 2.39, 95% CI 1.10–5.19). This is confirmed by another meta-analysis of 21 large studies. Also, the presence of chronic pathology of the respiratory tract prevailed in the group of patients with severe COVID-19 (12%), compared with the group with a milder course (4%).

Regarding COVID-19 mortality, mixed results have been reported. One meta-analysis<sup>4</sup> found that COPD and bronchial asthma do not significantly influence mortality rate from COVID-19, whereas another meta-analysis found a higher mortality rate from COVID-19 in patients with COPD (38.5%) than in the control group (7.4%). In conclusion, these data show that pre-existing COPD is a risk factor for severe clinical courses of coronavirus infection, but, regarding the mortality risk, more data are needed.

There are several possible reasons why the epidemiological data from some countries suggest lower prevalence of asthma in patients with COVID-19. Many patients with asthma are under relatively close medical surveillance owing to the chronicity of the disease, and therefore these patients are more cautious about viral infections. Furthermore, anti-inflammatory drugs, such as corticosteroids, given to patients with asthma may have a protective effect, although this remains a matter of debate. Genetic differences may also account for differences in susceptibility to severe COVID-19. Another issue might be the sometimes imprecise documentation of comorbidities among patients who were hospitalized or treated in the ICU, which leaves some uncertainty with regard to the true prevalence of asthma within this group.

More importantly, there are now increasing data indicating that the type of inflammation in asthma may play an important role in the risk of SARS-CoV-2 infection. Asthma, particularly in the paediatric population, is mostly associated with type 2 inflammation, which is characterized by a dominance of T helper 2 (T<sub>H</sub>2) cells and their hallmark cytokines IL-4, IL-5 and IL-13, and eosinophilia. IL-13 has been shown to downregulate the expression of the SARS-CoV-2 host cell entry receptor angiotensin-converting enzyme 2 (ACE2) on airway epithelial cells, and reduced levels of ACE2 transcripts have been associated with allergy, allergen exposure and high IgE levels<sup>5,6</sup>. Also, ACE2 gene expression correlates negatively with type 2 biomarkers, such as allergen-specific IgE and fractional exhaled nitric oxide<sup>7</sup>, and the lowest levels of ACE2 mRNA have been detected in patients with both allergic sensitization and asthma. Eosinophils depend on the T<sub>H</sub>2 cell-associated cytokine IL-5 for their survival and function. They express Toll-like receptor 7, which recognizes single-stranded RNA, triggering an activation pathway that enhances the antiviral effects of eosinophils<sup>8</sup>. Eosinophilia is negatively associated with COVID-19 susceptibility, whereas eosinopenia is a biomarker of severe COVID-19. Also, mast cells,

the other major allergy-associated effector cells, have high antiviral potential owing to their production of interferons and other antiviral mediators. In combination, these and other mechanisms<sup>9</sup> associated with type 2 inflammation may reduce the risk for severe COVID-19.

This is in contrast to mechanisms associated with non-type 2 asthma and COPD, which show a dominance of T<sub>H</sub>1-type or type 1 cytotoxic T (T<sub>c</sub>1)-type responses and T<sub>H</sub>17 cell activation. This type of inflammation is associated with an increased expression of ACE2, although the underlying mechanisms are not fully understood<sup>5,7,9</sup>. Furthermore, many patients with non-type 2 asthma or COPD suffer from other comorbidities that are associated with chronic low grade inflammation<sup>10</sup>, and this may predispose to a more severe course of the disease.

The relationship between SARS-CoV-2 infection and patients with chronic inflammatory lung disease is a complex one. In contrast to the initial perception that chronic inflammatory lung disease would constitute a risk factor for severe COVID-19, at least for study cohorts in many countries this is not the case for asthma. Bronchial asthma seems to represent a unique chronic inflammatory lung disease, as patients with COPD show an increased risk pattern for more severe COVID-19. Also, although many respiratory viruses cause acute asthma exacerbations, this seems not to be the case for SARS-CoV-2. One possible explanation for this diverse disease pattern may reflect different asthma endotypes. Patients with type 2 asthma exhibit a reduced risk for severe COVID-19. However, more work is needed to fully understand the unique and complex association between SARS-CoV-2 and asthma.

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#### Competing interests

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