



Is asthma a risk factor for coronavirus disease-2019 worse outcomes? The answer is no, but . . .

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Purpose of review

To search for evidence on whether having asthma increases the risk of poor outcomes of COVID-19 and report on recommendations on optimal asthma management in times of COVID-19.

Recent findings

Patients with asthma are neither at greater risk of becoming infected by SARS-CoV-2 nor they are at risk of complications of COVID-19 but those requiring frequent use of oral corticosteroid may be at greater risk.

Summary

In general, patients with asthma are not at risk of COVID-19 morbidity or mortality. On the contrary, patients with asthma may be at lower risk of hospitalizations during the COVID-19 pandemic. This may be related to asthma and its treatment, to patient's behavior, to the health system, and to collective changes in activities. It is likely that reduction in respiratory infections because of social distancing, face masks, and hand washing have a role in the reduction in asthma hospitalizations. Management of asthma in times of COVID-19 must be optimized, medication have to be used regularly and exacerbations detected early. Systemic corticosteroids may be used for control of severe asthma or severe exacerbations. Patient education on an action plan is crucial, as well as facilitating communications with the healthcare team.

Keywords

asthma, coronavirus disease-2019, multimorbidity, risk factors

INTRODUCTION

Lung diseases affect millions of people of all ages and levels of socioeconomic status. According to the Global Burden of Diseases (GBD) Study 2019, there were estimated 262 million cases and 461 000 deaths because of asthma in 2019 [1]. Hence, globally, over 1000 people die from asthma every day. Most of these deaths are premature and preventable with proper and timely management [2].

The novel coronavirus disease-2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. The WHO declared the COVID-19 outbreak a pandemic on 11 March 2020, demanding effective national and global mitigation measures and strong public health response [4]. Since 31 December 2019 and as of 30th December 2020, 80 316 555 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported, including 1 770 695 deaths [5].

The major question we were asked is whether having asthma increases the risk of poor outcomes of COVID-19. The straight answer is no, but the most severe cases requiring frequent doses of oral

corticosteroids may be at higher risk as we will discuss in this article. The review encompasses a hot and evolving topic, in which the evidence from longitudinal studies is scarce but comes up in novel reports daily. We ask the readers to understand the limitations of this article, which include publications available up to 31 December 2020 only.

IS ASTHMA MORE OFTEN ASSOCIATED WITH SEVERE CORONAVIRUS DISEASE-2019?

Viral infections are the most frequent causes of exacerbations in patients with chronic respiratory diseases. Considering the high prevalence of asthma

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KEY POINTS

- In general, patients with asthma are neither at increased risk of getting infected by the SARS-CoV-2 nor for poor outcomes of COVID-19.
- There is evidence of reduced hospitalizations because of asthma during the pandemic, which is likely an effect of reduced frequency of acute respiratory infections because of behavior aiming at COVID-19 prevention.
- Treatment of patients with asthma and rhinitis must be optimized to minimize the requirement for oral corticosteroids and need for emergency care.

and the astonishing spread and exponentially increasing incidence of COVID-19, and the potential harm respiratory viruses may produce to patients with asthma, there were reasons for major concerns at the beginning of the pandemic. But so far, asthma has not been consistently identified as a frequent comorbidity associated with COVID-19 hospitalizations or deaths. A report by leaders of the WHO Global Alliance against Chronic Respiratory Diseases [6[¶]], highlights the varied frequencies of comorbid asthma observed in COVID-19 patients. In Wuhan it was 0.9%, [7], whereas a higher frequency of 9% was reported among the US COVID-19 patients [8]. In the UK, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) reported 14,5% of hospitalized COVID-19 patients have asthma [9[¶]]. In the State of Sao Paulo, Brazil, according to reports

of the Health Department, the frequency of asthma among 42 788 individuals who died with COVID-19 in 2020 was 3.1%, much lower than the reported prevalence of asthma in the Country. It was also 10 times less frequent than diabetes, observed in 43.3% [10].

People with asthma are not at increased risk of acquiring COVID-19. A systematic review did not show an increased risk of COVID-19 in people with asthma [11]. Handwashing, masks and social/physical distancing have reduced the incidence of other respiratory infections in 2020. As a result, many countries are seeing a reduction in asthma and COPD exacerbations. An analysis of the databases of the Public Health System of Brazil [12] performed for the purpose of this publication, comparing hospital admissions because of asthma from April to September 2019 to the same period of 2020, which represents the peak of the first wave of the epidemic, indicates the admissions because of asthma have been markedly reduced to less than a half in the entire Country and in each of its five geographic regions, as presented in Fig. 1. These unexpected and remarkable reductions in hospital admissions may be attributable to some protection provided by atopy [13], by protection related to the use of inhaled corticosteroids [14], or else by better adherence to treatment and preventive measures, and finally to fear of attending any health service or unavailability of beds. Therefore, the reduction in hospitalizations may not necessarily reflect a proportional reduction in morbidity but certainly argue against a higher risk of SARS-CoV-19 infection, worse outcomes of COVID-19 or deterioration of

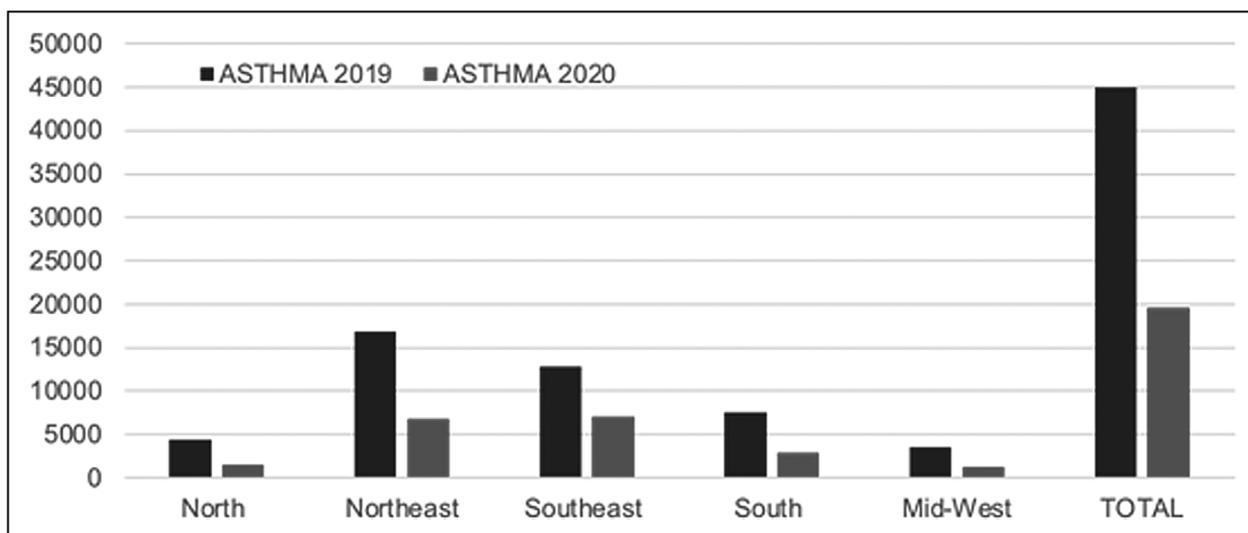


FIGURE 1. Hospital admissions because of asthma in the Public Health System in Brazil. A comparison of two periods: April to September 2019 (no COVID-19) and April to September 2020 (peak of the first wave of COVID-19). COVID-19, coronavirus disease-2019.

asthma control and exacerbations being associated with COVID-19 in patients with asthma.

MANAGEMENT OF ASTHMA AND ALLERGIC RHINITIS IN TIMES OF CORONAVIRUS DISEASE

While managing patients with respiratory diseases in times of COVID-19, it is critical to identify those patients with comorbid conditions of risk of poor outcomes of COVID-19, such as diabetes, arterial hypertension and obesity, for a more careful evaluation, surveillance and early intervention, particularly among the elderly. It is essential, as well, to have a precise diagnosis of asthma and to optimize the management of patients with uncontrolled, difficult-to-treat and severe asthma, who may have a higher risk of worse outcomes, either because of the airway disease severity itself or because of the frequent requirement of systemic corticosteroids [15¹¹]. Patients with difficult-to-treat or severe asthma need high doses of inhaled controller therapy, which may be associated with risk of pneumonia, and are more vulnerable to exacerbations, having a higher risk of morbidity and mortality [15¹¹].

A large study in the United Kingdom found that, overall, people with asthma are not at increased risk of COVID-19-related death. However, the risk of COVID-19 death was increased for people who had recently needed oral corticosteroids for their asthma [16¹²]. Therefore, it is important to offer proper asthma management and improve adherence to

treatment, with strategies to maintain good symptom control, reduce the risk of severe exacerbations and minimize the need for oral corticosteroids. Some reports have indicated having the asthma controlled may protect against complications of COVID-19, so that even patients using high doses of inhaled therapy with corticosteroids and biologic therapy, if controlled, may not have a worse prognosis. A large database analysis from Spain reports observations on 71 182 patients with asthma, 1006 (1.41%) of which have suffered from COVID-19. Patients with asthma and COVID-19 were older and at increased risk because of comorbidity-related factors. Inhaled corticosteroids and biologics were generally well tolerated and possibly associated with a protective effect against severe COVID-19 infection [17¹³]. A report from France, describes observations on a cohort of patients hospitalized for COVID-19 ($n = 768$) having a history of asthma ($n = 37$). None of them presented with an asthma exacerbation. The conclusion is that asthma patients were not overrepresented among those with severe pneumonia because of SARSCoV-2 infection who required hospitalization. The worst outcomes were observed mainly in patients with other major comorbidities [18¹⁴].

The Global Initiative for Asthma (GINA) has advised patients with asthma must continue taking their prescribed asthma medications, including inhaled corticosteroids, and for the severe cases, oral corticosteroids and biologics during the pandemic, if required, as summarized in Table 1 [19]. Oral corticosteroids may be used for exacerbations as

Table 1. Adapted from the Global Initiative for Asthma interim guidance about coronavirus disease-2019 and asthma updated on 20 December 2020

Medications	Advise patients to continue taking their prescribed asthma medications, particularly inhaled corticosteroids For patients with severe asthma, continue biologic therapy or oral corticosteroids if prescribed
	Make sure that all patients have a written asthma action plan, advising them to: increase controller and reliever medication when asthma worsens take a short course of oral corticosteroids whenever appropriate for severe asthma exacerbations
	Avoid nebulizers whenever possible, to reduce the risk of spreading virus Pressurized metered dose inhaler via a spacer is preferred except for life-threatening exacerbations Add a mouthpiece or mask to the spacer if required
Vaccines	Influenza vaccination Remind people with asthma to have an annual influenza vaccination
	COVID-19 vaccination Many types of COVID-19 vaccines are in development, and new evidence, including in people with asthma, will emerge over time In general, allergic reactions to vaccines are rare, current advice is that the Pfizer/BioNTek COVID-19 and Moderna vaccines should be administered in a healthcare setting where anaphylaxis can be treated if it occurs, and they should not be administered to patients with a history of severe allergic reaction to polyethylene glycol, or any other vaccine ingredient Current advice from the US Centers for Disease Control and Prevention (CDC) is that people who have received a COVID-19 vaccine should continue to wear a mask and avoid close contact with others At present, based on the risks and benefits, and with the above caution, GINA recommends COVID-19 vaccination for people with asthma

Data from [20]. COVID-19, coronavirus disease-2019; GINA, Global Initiative for Asthma.

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needed. It advises the avoidance of nebulizers whenever possible, to reduce the risk of spreading viruses. Pressurized metered dose inhalers via a spacer are preferred except for life-threatening exacerbations. A mouthpiece or mask may be added to the spacer if required. The use of nebulization for patients who need beta-agonists in an emergency is commonly preferred by many emergency units but its use potentially increases the risk of aerosolization and as the nosocomial transmission of respiratory pathogens which is a major threat in the context of the SARS-CoV-2 pandemic. Early treatment of exacerbation in asthmatic patients with increased dose of maintenance therapy associated with rescue therapy and possibly oral corticosteroid, can help to ensure that patients are less likely to deteriorate to the stage when nebulizers or emergency units are needed. In case of asthma exacerbations because of COVID-19, one shall note that silent hypoxia ('Happy Hypoxemia') has been described, in which oxygen saturation is influenced and overestimated by respiratory alkalosis that often occurs in COVID-19 patients [20]. So far, it has been observed that asthma is associated with prolonged intubation, but it is not associated with higher mortality, when mechanical ventilation is required in patients infected with SARS-CoV2 [21].

Regarding biologics approved for asthma treatment, possible effects on the risk of COVID-19 may differ. However, omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab reduce asthma-related exacerbations and have all been approved for the treatment of severe asthma. Approximately 80% of asthma exacerbations are related to viral infections. Thus, these effects on overall exacerbations suggest that biologics used for the treatment of asthma may protect against virally exacerbated disease. This effect has been best established for omalizumab, which prevents IgE from binding to its receptor on plasmacytoid dendritic cells [22].

With reference to allergic rhinitis, ARIA Initiative and the European Academy of Asthma and Clinical Immunology jointly recommend the regular use of intra-nasal corticosteroids in patients with chronic persistent allergic rhinitis, even when suffering from COVID-19 infection, as stopping the medication could result in more sneezing and increased spreading of the virus, in addition to the fact that exacerbation of allergic rhinitis might be confused with symptoms of COVID-19 [23].

It is noteworthy that adherence to treatment in patients with asthma and COPD during COVID-19 pandemic has increased [24]. The higher adherence to controller treatment among asthmatic patients seen during the pandemic may be one of the reasons

why asthma has not been an important risk factor for worse outcomes of COVID-19 infection.

A POSSIBLE PROTECTION RELATED TO ATOPY IN ASTHMA AND RHINITIS

SARS-CoV-2 enters the host cell through large spikes projecting from its envelope, which recognizes angiotensin-converting enzyme 2 (ACE2) receptors, particularly in the human respiratory epithelial cells. This process is dependent on the host serine protease TMPRSS2, which cleaves viral spike protein and allow viral and cellular membranes fusion [25,26]. Kimura *et al.* [27] demonstrated that IL-13, a cytokine associated with type 2 asthma, suppresses ACE2 expression in airway epithelial cells from patients with atopic asthma. According to these findings, it was hypothesized that ACE2 expression is modulated by type 2 inflammation in upper and lower airways. Allergic sensitization was inversely related to ACE2 expression on nasal epithelium, independently of asthma. Greater reductions in ACE2 expression in asthmatic children with moderate or severe allergic sensitization were noted when compared with children with asthma but without or with minimal allergic sensitization [13]. Furthermore, ACE2 expression was inversely associated with type 2 inflammation markers as allergen-specific IgE, total IgE, FeNO and IL13 expression in nasal epithelia. All of these observations support the hypothesis that the airways of patients with allergic asthma and atopic diseases express less ACE2 receptors, possibly leading to reduced entry of the virus in the host cells and being protective against SARS-CoV-2 infection and may indicate a pathway for the development of options for prevention. Furthermore, some studies reported inhaled corticosteroids are associated with decreased expression of ACE2 in induced sputum [14,28], which may also benefit patients with asthma and rhinitis on regular treatment.

POSSIBLE ADDITIONAL EXPLANATIONS FOR REDUCED ASTHMA HOSPITALIZATIONS IN TIMES OF CORONAVIRUS DISEASE-2019

The possible explanations for the reported reduction in asthma exacerbations during the COVID-19 pandemic in 2020 can be divided into four categories, as shown in Table 2: those related to asthma and its treatment, such as reduced expression of ACE2 receptors in atopics and the potential protection by inhaled corticosteroids; related to patient's behavior, such as better adherence to treatment or fear of attending emergency health services, use of

Table 2. Possible explanations for reduced asthma hospitalizations in times of coronavirus disease-2019

Related to asthma and its treatment	Lower risk of infection associated to reduced expression of ACE2 receptor in the airways: of atopics of patients using nasal topical or inhaled corticosteroids
Related to patient's behavior	Better adherence to treatment and preventive measures Social distancing, careful use of face masks and hand washing Fear of attending emergency health services
Related to the health system	Reduced availability of hospital beds Lower priority to asthma
Related to collective change in pattern of activities	Reduced urban traffic and air pollution Reduced travelling Home office practices Closing of schools

ACE2, angiotensin-converting enzyme 2.

face masks and hand washing; related to the health system, such as reduced priority to asthma and availability of beds; related to collective changes in pattern of activities, such as better air quality, as a result of reduced traffic and air pollution, or social distancing by reduced travelling, closing of schools and home office practices.

The observed lower levels of air pollution during this pandemic (Barcelona, Dehli, Rio and others) [29–31] and the extreme measures to avoid transmission of respiratory viruses likely reduced morbidity and mortality because of respiratory diseases unrelated to COVID-19, particularly those associated to acute respiratory infections, so often the cause of asthma exacerbations [32]. The population in general was afraid of attending health services during the peak of the pandemic, which could potentially increase morbidity and mortality in case of severe exacerbations. Priority of beds and attention to COVID-19 cases could worsen the situation of patients with asthma in case they seek emergency care. But this is not what we have observed among our patients (unpublished preliminary observations). There have been no reports from other centers indicating increased mortality because of asthma either.

IS THERE A PLACE FOR TELEMEDICINE FOR ASTHMA MANAGEMENT DURING THE PANDEMICS?

In this challenging scenario of high prevalence of asthma and an epidemic of a novel and potentially lethal and highly contagious viral respiratory infection, telemedicine can be an option to maintain medical monitoring during the pandemic, helping reducing patients' anxiety and stress, maintaining the asthma control and minimizing the risk of transmission. However, there are limitation to assessment without visual clues and when equipment, such as a pulse oximeter or peak flow are not available to

objectively evaluate the patients. For mild cases, assessment via telephone or video may be enough, but evaluation by video must be used preferentially to approach patients with acute symptoms and greater risk [33]. We often need to differentiate whether the patient has an exacerbation of asthma or COVID-19. It is not always simple even in a regular consultation. Both can present with cough and breathlessness, but specific features may indicate COVID-19, such as fever, onset of dyspnea between 4 and 8 days into the illness, flu-like symptoms and absence of wheezing [34].

CONCLUSION

There are neither consistent evidence that patients with asthma are at greater risk of becoming infected by SARS-CoV-2 nor that they are at greater risk of having poor outcomes of COVID-19. On the contrary, there are reports indicating patients with asthma may be at lower risk of hospitalizations during the COVID-19 pandemic. The reasons behind these observations may be various, related to asthma and its treatment, related to patient's behavior, related to the health system and related to collective changes in pattern of activities. It is likely that reduction in acute respiratory infections because of social distancing, use of face masks and hand washing has a major role in the observed reduction in asthma hospitalizations because of the prevention of common colds. Management of asthma in times of COVID-19 must be optimized, medication has to be used regularly and exacerbations shall be detected early to be halted. Systemic corticosteroids may be used as required, for control of severe asthma or severe exacerbations. Patient education on an action plan for asthma attacks is crucial, as well as facilitating communications with the healthcare team for unscheduled visits or teleconsultations. Observations from the pandemic scenario on different causes for the

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reduction in asthma morbidity must be investigated to inform future strategies for prevention of asthma attacks.

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Conflicts of interest

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