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To cite this article: Agamemnon Bakakos & Anastasia Krompa (2021): Asthma in the era of SARS CoV-2 virus, Journal of Asthma, DOI: [10.1080/02770903.2021.1941093](https://doi.org/10.1080/02770903.2021.1941093)

To link to this article: <https://doi.org/10.1080/02770903.2021.1941093>



Published online: 21 Jun 2021.



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Asthma in the era of SARS CoV-2 virus

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ABSTRACT

Objectives: It is well established in international literature that respiratory viruses can trigger asthma exacerbations. However, not all viruses affect patients in the same manner and extent. The pandemic of the SARS CoV-2 virus has brought interest to study the association of this novel virus on patients with mild-moderate and severe asthma in terms of susceptibility, severity and treatment.

Data sources – study selection: We performed an extensive search of current literature in the databases PubMed, Scopus and Google Scholar for original articles. We decided to include all types of articles, except for case studies, published until the end of February 2021 focusing on the effects of COVID-19 on the respiratory system and the main treatment recommendations up to date for patients with bronchial asthma.

Results: Until now there is no clear evidence that asthmatics have a higher risk of experiencing exacerbations when infected, nor higher mortality rates than the general population. Nevertheless, our knowledge on molecular pathways behind asthma phenotypes in the past decades is growing, and it underlines the need to predict the unique response each patient may have to infection from the novel coronavirus. It is not clear yet if certain sub-populations of asthmatics are at higher risk than others.

Conclusion: Despite the lack of evidence for higher susceptibility and/or mortality in relation to COVID-19, all asthmatic patients, whether treated with inhaled bronchodilators/corticosteroids or even biologics, should maintain their controller therapy without making any alterations.

ARTICLE HISTORY

Received 22 February 2021

Revised 2 June 2021

Accepted 4 June 2021

KEYWORDS

Asthma; respiratory disease; coronavirus; COVID-19; SARS CoV-2 virus

Introduction

Asthma is a complex respiratory syndrome affecting people of every age and social status around the globe, with an estimated prevalence of around 350 million people. It ranges from barely noticeable symptoms to severe impairment of patients' life and even life threatening events (1). Most patients should receive an inhaled corticosteroid (ICS) - containing controller treatment to reduce the risk of serious exacerbations, but a small percentage of asthmatics require oral corticosteroids (OCS) or even monoclonal antibodies, in order to contain the burden of the disease (2). Since the appearance of the novel SARS COV-2 virus in the early 2020, many comorbidities have been recognized to worsen the outcome of the disease, such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus and obesity. It is widely accepted that although COVID-19 is a systemic disease which triggers a cascade of both inflammation

and hypercoagulation, asthma per se, especially when not treated properly, may make the difference between being treated as outpatient and the need for hospitalization and even intubation along with mechanical ventilation (3). Respiratory viruses have been attributed as one of the main causes of asthma exacerbations. Therefore, it is crucial to determine whether asthmatics are in greater danger of being infected with the SARS COV-2 virus, of experiencing milder or more severe symptoms than the general population, and of having asthma exacerbations due to the novel virus. Additionally, it is of utmost importance to underline that all asthmatic patients are not the same. Asthmatics have different endotypes, which simply means the presence of a distinct pathophysiological mechanism that leads to the common features of airway hyper-responsiveness, remodeling and inflammation (4). Accordingly, it is interesting to explore the differences that might occur along those unique patient subtypes

and highlight the possible changes that the pandemic might bring to their presentation and management (5). The aim of this review is to explore the association of SARS-CoV-2 with asthma in terms of pathogenesis, susceptibility, severity and treatment.

Materials and methods

Inclusion criteria

For inclusion in this review, articles had to provide an insight in the management of asthma patients and shed light in the maze of cytokines and inflammatory

factors that are strongly linked with both asthma and coronavirus infection. We decided to include all types of articles with no restrictions, except for case studies. Articles that were not written in English language and non-peer reviewed articles were excluded (Figure 1).

Search methods

We performed an extensive search of the current literature in the databases PubMed, Scopus and Google Scholar for original articles. The last search was carried out on February 23rd of 2021. Two independent reviewers carried out the research using the following

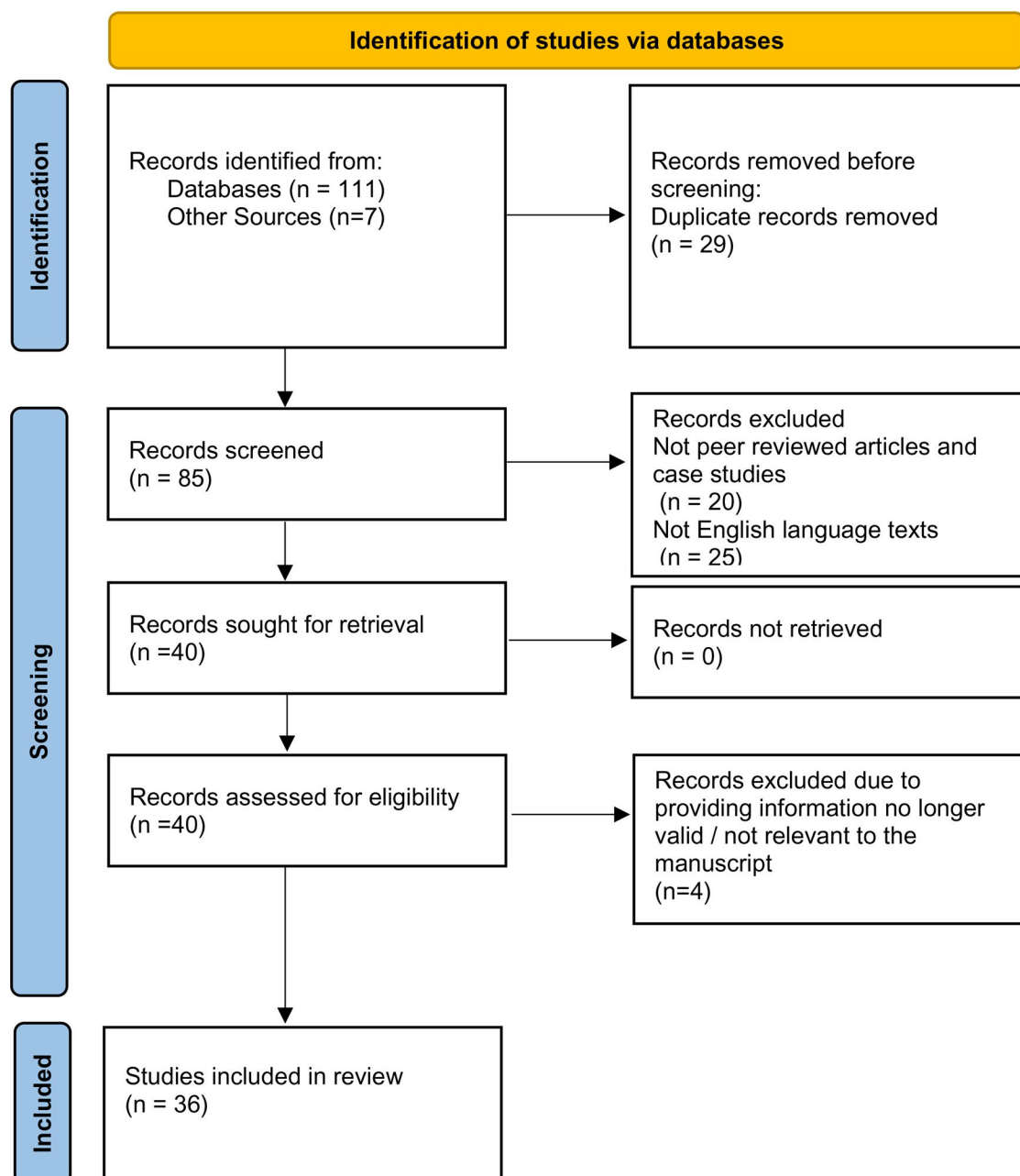


Figure 1. Study flow chart.

keywords in multiple combinations: “coronavirus,” “COVID-19,” SARS CoV-2” and “asthma.” Search results were initially screened based on their title and abstract by both authors. Secondly, the full text of the articles was extracted and assessed in detail in order to determine whether it met the inclusion criteria.

SARS COV-2: infection of the lower respiratory tract

The novel coronavirus, SARS-CoV-2, recently emerged and began to infect humans in November 2019 causing high rates of respiratory disorders globally with COVID-19 being declared a pandemic by WHO in March 2020 (6). Transmission among individuals includes direct inhalation of contaminated droplets released into the environment mainly by sneezing or coughing, and contact transmission via oral, nasal, and eye mucous. Similar to SARS-CoV-1, the functional receptor of SARS-CoV-2 is considered to be ACE2 in the host cell. The virus's spike glycoprotein complex is attached to the aforementioned receptor permitting its fusion, intracellular entry, further replication and infection. Interestingly, compared to SARS-CoV-1, the novel coronavirus SARS-CoV-2 spike glycoprotein presents a 10 to 20-fold higher binding affinity to ACE-2 (7). ACE2 receptor, which is a homolog of angiotensin- converting enzyme (ACE), is expressed in nearly all human organs (7). Type II alveolar cells show the highest ACE2 expression, while the surface of epithelial cells in the oronasal mucosa and nasopharynx are much weaker. Moreover, the expression of ACE2 is ample on myocardial cells, proximal tubule cells of the kidney and podocytes, bladder urothelial cells, and enterocytes of the small intestine, especially in the ileum (7,8).

A variety of factors such as age, sex, several co-morbidities, diabetes mellitus and cardiovascular disease have been associated with both altered ACE2 expression and COVID-19 severity. Following the infection path, viral incubation period is considered approximately 3–14 days. The presence of COVID-19 manifests by a range of symptoms, from asymptomatic/mild ones to severe illness and death. Although the disease manifests with common clinical cold symptoms of “fever, cough, fatigue, loss of taste, and olfaction” and it mainly affects the lower respiratory tract, other systems can also be involved such as GI, causing diarrhea. Diagnosis of COVID-19 is based on molecular diagnosis of viral genome by RT-PCR and may be assisted by clinical signs and symptoms, laboratory blood tests, epidemiologic history and

radiologic imaging. Typical laboratory features include lymphopenia, elevated levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, d-dimers, cardiac biomarkers, aspartate aminotransferase and decreased albumin (8,9). Approximately, 10–20% of patients suffer from a more severe form with pneumonia defined as bilateral ground glass opacities in CT scan and ARDS requiring hospital admission or even intensive care unit (ICU) treatment with overall worldwide mortality 6.7%. Aberrant proinflammatory mediators' secretion with cytokine storm has been implicated as a prominent feature of severe SARS-CoV-2 infection with excess activation of monocytes, macrophages, megakaryocytes, dendritic cells and activation of the coagulation cascade on endothelial surfaces of small blood vessels. Similar to the pathological features of SARS and MERS, severe diffuse alveolar damage, such as extensive edema, hyaline membrane formation, inflammatory infiltrates, microthrombi formation, organization, and fibrosis, was also observed in severe COVID-19 (9).

Currently, patients with moderate to severe asthma are classified by CDC as a high-risk group, susceptible to severe COVID-19. Asthma exacerbations can be triggered by viral infections among other causative factors such as allergen contact, exercise and anxiety. Thus, it is reasonable to treat patients presenting with acute exacerbation symptoms as possible COVID-19 cases until results from molecular and imaging techniques are obtained (10). The degree of risk and associated clinical outcomes for people with asthma, however, are not clearly understood on the basis of available data.

SARS COV-2 and the cytokine response in asthma

In the pathogenesis of both asthma and COVID-19, a complex pathway of pro-inflammatory cytokines has been implicated. It is common knowledge that viral infections are able to trigger asthma exacerbations, but it remains unclear whether asthmatic patients are more susceptible than general population to severe SARS-CoV-2 infection and its complications. The impact of asthma remains particularly controversial, ranging anywhere from protective effect to risk for worse outcomes in non-T2 high asthmatics (11).

Cytokine storm (CS) caused by dysregulated and exaggerated immune response has been described in a growing body of clinical data regarding more severe and fatal cases of COVID-19 and it is, also, considered to be the determinant of pathological alterations and the clinical manifestation of ARDS (12). CS is related

to severe lymphopenia, thrombosis, and massive mononuclear cell infiltration in multiple organs (13). As previously mentioned, the intracellular entry of SARS-CoV-2 is highly dependent on the binding of the S protein to the cellular ACE2 receptor. This binding is primed by TMPRSS2 (Transmembrane protease, serine 2) (12,14). Once entering the respiratory epithelial cells, the virus triggers an immune process accompanied of a somewhat weak interferon response. TH1 cells seem to have a pivotal role in this process. Notably, they secrete pro-inflammatory cytokines, mainly granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), interleukin-6 (IL-6), which further activate monocytes. Monocytes and macrophages induce production of tumor necrosis factor- α (TNF- α), IL-6 and monocyte chemoattractant (such as CCL2, CCL7, and CCL12) (15). Along with other pleiotropic cytokines, IL-6, drives an acute phase response that elevates serum ferritin, complement, CRP, and pro-coagulant factors. It is noteworthy that further increase in the levels of IL-1, IL-10, IL-6, and IL-8 is associated with an upregulation of ACE2 receptor. Membrane-bound immune receptors (e.g. Fc and Toll-like receptors) may, also, contribute to an imbalanced inflammatory response. Moreover, T_H2 cells have a part in modulating the ACE2 receptor in airways and regulating TMPRSS2, mainly through IL-13 (16). NF- κ B activation has been implicated through angiotensin II pathway, which also induce IL-6, vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1) and IL-1 (12). Rapid viral replication and rampant chemokine release, also induce and accelerate programmed cell death in lung epithelial and endothelial cells. IFN- $\alpha\beta$ and IFN- γ induce inflammatory cell infiltration through mechanisms involving Fas– Fas ligand (FasL) or TRAIL–death receptor 5 (DR5) and cause the apoptosis of airway and alveolar epithelial cells (15). Finally, weak IFN-I induction caused by viral proteins may also be an important amplifier of cytokine production and simultaneously, an impedance of immune system activation against the virus.

Asthma and its exacerbations, on the other hand, have another extensive network of cytokines implicated, the elaborate reference of which is beyond the scope of this article. Roughly, asthmatic patients have four main endotypes: T2 high/eosinophilic, Th17/neutrophilic, Th2/Th17/ mixed inflammation and pauci-granulocytic (17). T2/ eosinophilic type is correlated with the production of IL-4, IL-5 and IL-13, which are thought to downregulate ACE2 receptor in nasal and bronchial epithelium. Although T2-high asthma has been associated with more frequent

exacerbations it constitutes an immune response that is not involved in the immune defence against viruses. Nonetheless, a subset of severe patients exhibits a TH1- polarized immune response typified by increased IFN- γ . Accumulating evidence indicates that eosinophilia might have antiviral activity too, with patients presenting with fewer peripheral blood eosinophils displaying worse disease prognosis. Furthermore, peripheral blood eosinophil levels have been reported to gradually increase in recovering patients before discharge, accompanied by an improved clinical status (18). The above findings raise the possibility that allergy might be a protective factor for COVID-19, however further studies need to be conducted (18). IL-17A, IL-12 and TNF are the main mediators in Th17/neutrophilic asthma and are capable of upregulating ACE2 expression *in vitro* (19). Thus, it is clear, that the correlation between ACE2 receptor and the risk asthmatic patients face with SARS-CoV-2 infection is intricate.

Treatment of asthma in the SARS COV-2 era

The greatest issue healthcare providers experience around the globe during this pandemic is the extremely high danger of viral transmission when patients require nebulized medication, since it is a procedure with high aerosol generation potential (20). Numerous infections of healthcare staff have been already reported, especially in Italy, during procedures which create viral aerosol such as tracheal intubation and nebulization (21).

Levin et al. propose an interesting modified asthma treatment algorithm in order to avoid when possible nebulized therapy unless patients experience life threatening-events. Instead, they highlight the possibility of using metered-dose inhalers with spacers (concurrently with oxygen when needed), which have already proven to be non-inferior -especially in research data including children- in patients that visit the emergency department with an asthma attack and an unknown status of COVID-19 infection (22). The use of intravenous magnesium sulfate and oral corticosteroids is also proposed in order to further decrease the need of nebulizers. They acknowledge, however, that data is still scarce and in case nebulized treatment delivery is an absolute necessity, it is strongly recommended to be performed while all healthcare staff wear at least a N-95 mask and personal protection equipment. Finally, they conclude that all patients should continue their control therapy in order to minimize the risk of exacerbations (22).

Around 5% of all asthmatics require high dose combinations of ICS/LABA and oral corticosteroids, with some of them even receiving monoclonal antibody treatment, thus comprising the sub-group of severe asthma. Discussion on how steroids affect a possible infection from COVID-19 and whether patients receiving biologics should continue treatment shows great interest.

Corticosteroids, whether in an inhaled or oral tablet form, have been reported in the past as a predisposing factor of viral respiratory tract infections, possibly due to the reduction they cause to the recruitment of neutrophils in sites of inflammation (23). Nevertheless, there is no evidence yet that they increase the chance of infection from SARS CoV-2 or the severity of the disease.

In a recent *in vitro* study, ICS were even reported to have a protective effect against the novel virus, especially ciclesonide and mometasone, by inhibiting the replication of the viral nonstructural protein 15 (NSP-15) in MERS and SARS-CoV-2. However, the generation of resistant mutations might preclude clinical effect (24). Similar results were reported in another *in vitro* study, as Yamaya et al. demonstrated that budesonide paired with bronchodilators, either formoterol or glycopyrronium, can act protectively against the coronavirus HCov-229E by halting its replication and cytokines production. Regarding OCS, data is still scarce due to the small number of patients who still rely on them for severe asthma control. Most severe asthmatics presenting a T2 high endotype are able to reduce or even stop OCS with the use of biologics that are corticosteroid sparing such as omalizumab, mepolizumab, benralizumab and dupilumab (25). After early skepticism over the use of corticosteroids, the RECOVERY trial enrolled a total of 6,425 coronavirus positive hospitalized patients who were divided in groups that received standard care with or without the addition of dexamethasone. The subgroup that received corticosteroids demonstrated a lower mortality rate after a 28-day period compared to the usual care group, with the results being most notable in patients that needed mechanical ventilation or oxygen support. These results, although preliminary, imply that corticosteroids and more specifically dexamethasone can be beneficial in critically ill patients. Unless proved otherwise, we can believe that asthmatics follow the same rule and can be benefited by the use of oral corticosteroids in the setting of severe illness by COVID-19 (26). Current guidelines from experts and major respiratory societies such as GINA don't recognize a particular danger from continuing ICS or OCS as controller treatment and

underline the importance of maintaining patients in the lowest possible oral corticosteroid daily dose (25). Moreover, they strongly advise against the discontinuation of any medication without consulting a health-care provider. It should be stressed that in a pandemic situation many patients can abruptly stop their treatment due to misinformation from the media or the Web and doctors should be prepared to reassure those patients.

In patients who turn out positive for COVID-19 the situation is even more unclear. The WHO has discouraged the use of systemic corticosteroids in the treatment of mild-moderate SARS-CoV 2 infection, but experts around the world and emerging retrospective studies suggest that in patients with severe symptoms or ARDS systemic corticosteroids may play a pivotal role, especially in preventing the fatal cytokine storm syndrome (27,28). Yet again results are contradicting and hard to interpret, since in a randomized double-blind phase IIb study which treated COVID-19 positive patients in a 5 day regime with either methylprednisolone 0.5 mg/kg or placebo, researchers found that systemic corticosteroids did not reduce mortality rates after 28 days and 2 months or hasten the virus clearance in the respiratory tract after 7 days (29). Therefore, we can summarize that asthmatics on ICS and OCS should continue their treatment as usual. If they are found positive for the coronavirus, treatment options should be personalized depending on the severity and symptoms of their disease.

Biologics are the newest weapon in our arsenal for severe asthma and many patients have found their effects to be lifesaving, not only because of the quality of life they offer, but also due to their steroid sparing effects, which release patients from the burden of the numerous side effects of corticosteroids. Omalizumab is the oldest monoclonal antibody, an anti – IgE agent and mepolizumab, an anti-IL5 agent, are the most prevalent biologics of the newest generation of biologics. The other three monoclonals licensed to date are benralizumab, reslizumab and dupilumab (30).

In order to assess their efficacy during the pandemic it is sound to assess them in two groups. Mepolizumab, benralizumab and reslizumab interfere with IL-5 and the IL-5 receptor, thus depleting the eosinophil population in the lungs and peripheral blood of patients, reducing the T2 inflammation (30). Consequently, the question that arises would be: "Do eosinophils play a role in the pathogenesis of SARS CoV-2?" Data until now is scarce regarding the association of COVID-19 with eosinophils and T2 cytokines. The only virus that has been shown to relapse

in patients under mepolizumab is herpes zoster virus in the COLOMBUS study, nevertheless the biologics have demonstrated an excellent safety profile in all the follow up studies. The sole gray zone is that no patient has been followed up for more than 4–5 years, which makes scientists less confident in ruling out any long-term side effects (31). Furthermore, the study COSMOS, which along with COLOMBUS are the most important follow up assessments of mepolizumab, has not remarked an increase in viral infections when comparing mepolizumab to placebo (32). We can assume that patients under those biologics can safely continue their treatment.

The second group is comprised by omalizumab and dupilumab, agents that inhibit T2 immunity. Omalizumab is mainly used for allergic asthma, since it binds to IgE and diminishes its levels. Studies have demonstrated that depleting IgE might also prove beneficial in patients by reducing the prevalence of viral diseases of the upper respiratory tract. More specifically, the PROSE study tested children aged 6–17 years old with allergic asthma and randomized groups to receive either omalizumab or standard asthma care for a 90-day period during the fall of two consecutive years. Results showed that the group under biologic treatment had reduced incidence of infection from rhinoviruses, reduced duration of illness and a faster viral shedding period (33). Concerning dupilumab, the unique monoclonal antibody targeting both IL-4 and IL-13, our expertise is still lacking since it is only available for almost 2 years for the treatment of severe asthma in the U.S. The producing company suggests that “there is no evidence it increases the risk of COVID-19 infection” and underlines that concerning its off-label use “physicians should use their own medical knowledge and discretion.” Furthermore, patients with atopic dermatitis undergoing treatment with dupilumab in Bergamo, Italy, a region with a great coronavirus burden, showed neither higher susceptibility to infection nor higher mortality rates than the general population (34).

Patients receiving monoclonals used to receive the injection in daily clinics, but the pandemic has turned an otherwise totally safe procedure to a hazardous one, due to the number of patients simultaneously present in clinics. Recently the U.S. Food and Drug Administration has released a statement which approves the injection of biologics at home, in an effort to minimize the risk of coronavirus outbreaks in the setting of daily clinics. The same proposal has been made by the British Thoracic Society (BTS) and the Italian Society of Asthma Allergy and Clinical Immunology (SIAAIC). This is yet another sign that

the scientific community continuously adapts to the situation and strives to find the best solution for the patients (35,36).

Recommendations regarding asthma treatment in the COVID-19 era are presented in Table 1.

Conclusion

To summarize, it is evident that the sudden impact of SARS CoV-2 in our lives is far from being controlled. As for patients living with asthma, the objective remains the same: minimize the risk of exacerbations with the lowest possible dose of ICS/LABA, OCS or even biologic treatment. It is pivotal to adapt the methods of treatment to the current state of the pandemic, whether this requires the use of spacers in order for the patients to safely receive inhaled medicine in the state of an emergency or home-injections of biologics. Corticosteroid use received much criticism in the early stages of the pandemic, but latest evidence implies that they might even be beneficial for those with severe coronavirus infection or need of supplemental oxygen. Many unanswered questions still linger concerning the pathogenetic mechanisms of COVID-19 and how they may implicate specific asthma endotypes. We believe that there will be time to further research these special categories, however, for the time being it is of utmost importance that all healthcare providers reassure patients for the safety of continuing their control treatment of asthma. In the meantime, although asthmatics do not seem to encounter a higher risk of disease severity and/or mortality we should attempt to collect more data, in order to enhance our arsenal

Table 1. Recommendations for asthma treatment during the SARS COV-2 outbreak.

ICS – SABA/LABA	OCS	Monoclonal antibodies
Treatment should not be discontinued (25)	Prompt initiation in the setting of asthma attack (22,25)	Treatment should not be discontinued (31,32,35,36)
Avoid nebulized therapy even in unknown COVID infection status if possible (22)	Dexamethasone reduces mortality in hospitalized COVID (+) patients (26)	Eosinophil role in COVID infection not yet clarified (18)
Deliver only by dose metered spacers for patients at the emergency department (22)	No evidence of worse outcome despite early skepticism (25,26)	No evidence of worse outcome (25,35)

Abbreviations: ICS, inhaled corticosteroids; SABA, short-acting beta agonists; LABA, long-acting beta agonists; OCS, oral corticosteroids.

with more information regarding the state-of-the-art management of asthmatic patients in situations of a pandemic, situations we might have never imagined to live in before the outbreak in Wuhan.

Declaration of interest

The authors declare no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this manuscript.

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