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Asthma and severe acute respiratory syndrome coronavirus 2019: current evidence and knowledge gaps

Sara M. Assaf[a], *Svitlana P. Tarasevych*[b], *Zuzana Diamant*[c,d,e,f], *and Nicola A. Hanania*[g]

Purpose of review
Although respiratory viruses are common triggers of asthma exacerbation, it is unknown whether this also applies to infection with SARS-CoV-2. Indeed, patients with asthma and allergy appear underrepresented in large reports of COVID-19 cases worldwide. In this review, we evaluate existing literature on this topic and potential underlying mechanisms for any interrelationship between asthma and COVID-19.

Recent findings
Data from several preclinical and clinical reports suggest a lower susceptibility for COVID-19 in patients with underlying type 2 airway inflammation including asthma that may be related to a reduced expression of ACE2 and TMPRSS2 receptors for SARS-CoV-2. Corticosteroids further decrease expression of the ACE2 and TMPRSS2 receptors, hence may also have a protective effect against infection with SARS-CoV-2. In addition, some studies suggest that the reported improvement in asthma control and a reduction in asthma exacerbations during the COVID-19 pandemic may be related to improvement in adherence to controller therapy and reduced exposure to triggers, such as other respiratory viruses and air pollutants. Recent data point towards differential susceptibility for COVID-19 among asthma patients based on their phenotype and/or endotype. On the basis of existing evidence, continuation with controller therapies is recommended for all patients with asthma. For patients with severe uncontrolled asthma infected by SARS-CoV-2, adjustment of controllers and biologics should be based on a multidisciplinary decision.

Summary
Underrepresentation of SARS-CoV-2-infected patients with asthma and related allergic diseases may be based on potentially protective underlying mechanisms, such as type 2 airway inflammation, downregulation of ACE2/TMPRSS2 receptors, reduced exposures to triggers and improved adherence to controller medications. Although it is imperative that control should be maintained and asthma medications be continued in all patients, management of patients with severe uncontrolled asthma infected by SARS-CoV-2 including adjustment of controllers and biologics should be discussed on an individual basis.

Keywords
asthma, biologics, coronavirus, corticosteroids, COVID-19, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

Since end of 2019, culminating evidence of a new coronavirus has been reported from several hospitals globally [1]. This severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originating in the city of Wuhan, capital of the Hubei province in China, has since spread worldwide causing an overwhelming pandemic of the coronavirus disease 2019 (COVID-19), which has thus far affected over 23 million people worldwide and took the life of almost one million of them [2].

Several risk factors have been identified for SARS-CoV-2 infection including host factors, such as old age, male sex and obesity as well as underlying comorbidities including cardiovascular disease,

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KEY POINTS

- No published evidence to date indicates that well-controlled moderate-to-severe asthma increases the risk for SARS-CoV-2 infection or hospitalization.
- Some studies suggest that certain phenotypes/endotypes of asthma, such as those with type2 low asthma may be at higher risk of SARS-CoV-2 infection than those with type 2 high disease; however, this needs further examination in prospective large cohort studies.
- Maintaining current therapy with controller medications including biologics is recommended in all patients with asthma during the COVID-19 pandemic.
- The ongoing use of inhaled corticosteroids does not increase the risk of hospitalization in patients with asthma with concomitant COVID-19 infection.
- The decision to continue or postpone biologic therapy in patients already infected with SARS-CoV-2 should be individualized to each patient based on multidisciplinary discussions.

hypertension, diabetes and certain lung diseases including chronic obstructive pulmonary disease (COPD) [3]. However, initial publications on populations with COVID-19 in Wuhan, did not report patients with concomitant asthma, allergic rhinitis or atopic dermatitis, despite a substantial prevalence of these diseases in the general population in that city [4,5,6▪▪]. In addition, although many viruses including rhinoviruses and other coronaviruses are well known to trigger asthma exacerbations [7], increasing evidence from clinical observations and mechanistic studies of COVID-19 cases do not support this for SARS-CoV-2 [8,9]. In this review, we evaluate current knowledge based on published literature on the impact of comorbid asthma, its phenotypes/endotypes and its therapy on the susceptibility to SARS-CoV-2 infection and subsequent morbidity/mortality to COVID-19. In addition, we provide a summary of current recommendation for asthma management in the era of COVID-19 pandemic.

POTENTIAL MECHANISMS OF THE INTERRELATIONSHIP BETWEEN SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION ON ASTHMA

Understanding the mechanisms of infection with SARS-CoV-2 at a cellular level should help elucidate clinical and demographic variables that may influence susceptibility to and severity of COVID-19. Although common respiratory viruses causing asthma exacerbation, especially rhinoviruses, use the ICAM-1 molecule – overexpressed within the allergic airways – as an entrance into the respiratory epithelial cells [10,11], the SARS-CoV-2 enters the host cells through the ubiquitously present angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors [12]. TMPRSS2 is a transmembrane protease, which primes and modifies the viral S protein contributing to cellular entry and promoting spread of the infection [13▪,14]. The overall low ACE2 expression reported in allergic patients and in children with or without comorbid asthma could partly account for their underrepresentation among COVID-19 patients [15]. Variability in gene expression of ACE2 and TMPRSS2 is thought to further characterize subgroups of patients at higher risk of COVID-19 morbidity and mortality [16▪▪]. With this objective, a recent study examined sputum RNA samples from patients with asthma participating originally in the Severe Asthma Research Program (SARP-3) where 60% of the participants had severe asthma as defined by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines [17]. Although no difference was seen in SARS-CoV-2 gene expression between healthy patients ($N = 79$) and patients with asthma ($N = 330$), the latter group showed differential gene expression according to some demographic features and comorbidities. Multivariate mixed effects models showed increased ACE2 and TMPRSS2 expression in African American men with asthma and comorbid diabetes mellitus. Interestingly, treatment with inhaled corticosteroids (ICS) was associated with reduced expression of ACE2 and TMPRSS2 [16▪▪]. Although these results need to be replicated in future large studies, they may help identify patients with asthma who are at higher risk of contracting COVID-19 disease and at higher risk of complications following hospitalization with COVID-19 [16▪▪]. Moreover, the association between ICS and SARS-CoV-2 gene expression needs further investigation in prospective trials to confirm and elucidate any protective role.

Other studies investigated the association between respiratory allergy, asthma and expression of ACE2. In recognition of the heterogeneity of asthma, a recent study examined the differential expression of ACE2 based on asthma inflammatory phenotypes. Interestingly, an upregulation of ACE2 expression was seen in the bronchial epithelium of patients with type 2-low (non-type 2) asthma [18▪▪]. In susceptible children, allergen sensitization (regardless of concomitant asthma) was inversely related to ACE2 expression in the nasal epithelium and inversely correlated to type 2 inflammatory

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biomarkers (FeNO, blood eosinophils and serum IgE) [19]. In addition, and in line with previous preclinical data, experimental allergen challenge reduced ACE2 expression in both the upper and lower airways in allergic patients with asthma [15]. An upregulation of the TMPRSS2 receptor expression in the presence of type 2 biomarkers was found in other studies [20]. To date, it is still unclear how the contradictory regulation of ACE2 and TMPRS2 expression in response to type 2 biomarkers drives susceptibility to infection with SARS-CoV-2.

On the basis of the above premise, another hypothesis postulated a link between eosinophilic type 2 asthma and COVID-19. Clinical characteristics of hospitalized patients with COVID-19 showed a decrease in blood eosinophil count or eosinopenia with worse prognosis associated with decreased counts [21,22]. Initially, it was thought that eosinophilic sequestration happens at sites of inflammation and explained the depletion of peripheral eosinophilia [23]. However, although depletion of peripheral lymphocytes seen in COVID-19 is indeed related to their massive migration into the lungs as seen in postmortem analyses, eosinophils were not found in the interstitial lung inflammation and their depletion may be partly related secondary to phagocytosis caused by the cytokine storm [24]. Therefore, a protective link between the type 2 inflammatory phenotype of asthma (characterized mainly by the presence of its effector cells, the eosinophils) and COVID-19 infection and a possible role of the type 2 inflammatory axis as a counterregulatory loop to the inflammation in COVID-19 was inferred although still needs further investigation [18▪▪].

SUSCEPTIBILITY OF PATIENTS WITH ASTHMA TO CORONAVIRUS DISEASE 2019 INFECTION

The question of whether patients with asthma are at higher risk of getting COVID-19 infection stems from previous data showing that viral respiratory infections including coronaviruses can trigger asthma exacerbations in children and adults [25]. In early data on COVID-19 from China, one series of 44 672 patients, chronic respiratory diseases including asthma were underrepresented with a prevalence of 2.4% compared with their prevalence in the general population of 6.9% [26]. Asthma prevalence in patients with COVID-19 was also lower than anticipated from population levels in data emerging from Canada, Taiwan and Hong Kong [27]. However, data from the United States have been inconsistent. A series from Chicago showed a high prevalence of asthma (14%) in a large cohort of patients hospitalized with COVID-19 ($N = 1526$); however, when adjusting for sex, age and comorbidities, no association between asthma and risk of hospitalization with COVID-19 was found [28]. In fact, preliminary data from New York from patients with COVID-19 showed that asthma was not in the top comorbidities [29]. Furthermore, although data reported from the US Center for Disease Control (CDC) showed a higher prevalence of asthma (17%) among COVID-19 hospitalized patients; these data were unadjusted for other comorbidities and did not clarify whether asthma was an isolated morbidity or part of a multimorbidity [30]. For instance, other comorbidities including obesity, hypertension, coronary artery disease and sleep apnea were at higher rates among patients with asthma hospitalized with COVID-19 infection suggesting that these conditions tend to be associated with asthma and have to be accounted for. Finally, data from a large cohort study performed in the United Kingdom, showed that 14% of admissions with severe COVID-19 had underlying asthma ($N = 16\,749$) where the prevalence of asthma in the general population is estimated to be 12% [31].

Given the above data, it is still unclear whether patients with asthma are at increased risk for COVID-19 infection. However, it is worth pointing out that, although patients with asthma were underrepresented in some of these studies, in others, higher percentages were attributable to other comorbidities and demographics not adjusted for. Moreover, recent insight indicates that COVID-19 risk may differ by asthma inflammatory phenotype/endotype which can also influence the severity of the disease [18▪▪]. It is important to keep in mind that it is often difficult to differentiate between asthma exacerbation symptoms (that can be triggered by COVID-19) and symptoms related to the infection itself. A summary of some of the published cohorts that reports prevalence of asthma is shown in Table 1.

Despite lack of sufficient evidence, the Centers of Disease Control (CDC) in the United States and the British Thoracic Society (BTS) issued warnings that patients with asthma may be at increased risk of contracting COVID-19 and suffer severe outcomes from the disease.

RISK OF MORBIDITY AND MORTALITY IN PATIENTS WITH ASTHMA WITH CORONAVIRUS DISEASE 2019

A look at the outcomes of patients with asthma during previous pandemics including the 2009 H1N1 pandemic showed that patients with asthma

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Table 1. Overview of cohort studies on patients with coronavirus disease 2019 and prevalence of asthma

Study	Total patients	With asthma	Population level prevalence	Percent patientswith asthma	With exacerbations	Comments
Grandbastien *et al.* (Belgium) [8]	106	23	6.5%	26.1%	6	Patients with asthma appeared not to be at risk for severe SARS-CoV-2 pneumonia. Moreover, SARS-CoV-2 pneumonia did not induce severe asthma exacerbation.
Zhang *et al.* (China) [5]	140	0	4.2%	0	0	No patients with asthma.
Grasselli *et al.* (Italy) [32]	1591	0	6.1%	0	Unknown	No patients with asthma.
Richardson *et al.* (USA) [29]	5700	479	7.9%	9%	Unknown	
Lovinsky-Desir *et al.* (USA) [33]	1298	163	7.9%	12.5%	Unknown	Asthma was not associated with adverse outcomes in severe COVID-19, regardless of age, obesity, or other comorbidities.
Docherty *et al.* (UK) [31]	16749	2345	12%	14%	Unknown	Asthma was not associated with mortality.
Argenzian *et al.* (USA) [34]	1000	113	Unknown	11.3%	Unknown	
Haberman *et al.* (USA) [35]	86	15	10%	17%	0	No hospitalizations with asthma noticed.
Petrilli *et al.* (USA) [36]	5279	786 [a]	11%	14.9[a]	Unknown	
Broadhurst *et al.* (USA) [37]	436	53	12%	12%	Unknown	Asthma does not appear to be a risk factor for intubation among hospitalized COVID-19 patients.

COVID-19, coronavirus disease 2019.
[a]Asthma and chronic obstructive pulmonary disease mixed population.

hospitalized with H1N1 influenza were significantly less likely to have a complicated hospital course (need for invasive ventilation and death) compared with those without asthma (US cohort of 473 patients) [38]. However, these data are difficult to interpret because of several limitations of the study. In the current pandemic, the cohort study in Chicago showed no difference in mortality between hospitalized COVID-19 patients with asthma and those without (3.6 vs. 4.9%, respectively) [28]. In another cohort from New York examining data from 6245 patients with COVID-19 (272 out of 6245 had asthma), patients with asthma were not found to be at higher risk of mortality [39]. In contrast, a database from the United Kingdom looking at electronic health records (EHR) of 17 million patients with COVID-19 did show an association between severe asthma and increased risk of death for hospitalized patients after adjustment for sex, race but not for all comorbidities. The hazard ratio was higher for patients with asthma with documented recent oral corticosteroid use (defined as $\geq$1 in the year before baseline), which is a marker of the severity of asthma [40]. Other data from United Kingdom, examined the UK biobank that includes 490 000 patients of whom 13% had asthma. The study demonstrated that asthma conferred a higher risk of worse outcomes when adjusting for sociodemographic confounders; however, relevant comorbidities were not adjusted for. This study also looked at the association between different phenotypes of asthma and COVID-19 infection. Interestingly, the risk was mostly related to non-allergic asthma [41]. In another study, asthma was not an independent risk factor for intubation of patients hospitalized with COVID-19 even after adjustment for other risk factors like BMI and age [37].

Overall, the association between asthma and worse outcomes from COVID-19 remains unclear. As aforementioned, asthma patients with type-2 low inflammatory phenotype may be at increased risk of worse outcomes related to COVID-19, given the upregulation of SARS-CoV-2 associated genes [18▪▪]. Future prospective studies are needed to help stratify patients with asthma according to their phenotype/endotype to identify those at higher risk

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of developing severe COVID-19 and who warrant a closer follow-up.

DIAGNOSTIC AND ASSESSMENT STRATEGIES OF ASTHMA DURING CORONAVIRUS DISEASE 2019 PANDEMIC

The assessment and management of patients with asthma can be difficult during this pandemic especially with the reduction in number of face-to-face encounters with health care providers. In fact, the overlapping symptoms of cough, shortness of breath and wheezing to a lesser extent, can make it challenging to differentiate between the two conditions. Adding to this challenge is the remote assessment of patients via telephonic visits. Limitations exist in terms of the visual cues that can be absent unless the visit is augmented with a video, and the difficulty to obtain objective assessments of the patients including oxygen saturation, lung auscultation and peak flow meter measurements. A thorough history (including contact inquiry) can help differentiate one condition over the other. For example, the improvement of symptoms with reliever inhaler, audible wheezing, diurnal variation, absence of fever and reduced peak flow meter readings, can indicate more an exacerbation of asthma [42,43].

Remote assessment of asthma through telehealth was previously examined but not in the context of a pandemic. The results from multiple systematic reviews and meta-analyses showed mixed results but overall, no evidence of harm. In an interesting study, a cohort of 7000 patients had an electronic monitoring of their controller and rescue inhaler use during the pandemic, and increased adherence of 15% was found in the controller medication use [44].

Disruption to the diagnosis of new cases of asthma can also exist during this pandemic. Traditionally, asthma diagnosis is based on clinical history and objective data from supportive testing. Pulmonary function testing, such as spirometry is an aerosol-generating procedure, which subsequently limits the capacity to perform them. Full personal protective equipment needs to be available in addition to infection control measures (negative pressure rooms) [45].

In addition to the above-mentioned barriers to the assessment of asthma, mood disorders can be unleashed or exacerbated during the pandemic. Compared with the general population, patients with asthma have a higher prevalence of anxiety and depression. With the COVID-19 pandemic, there is potential threat to exacerbate an existing mood disorder or cause a new one, therefore, affecting effective control of asthma [46].

MANAGEMENT CONSIDERATIONS OF ASTHMA DURING CORONAVIRUS DISEASE 2019 PANDEMIC

Managing exacerbations

Recent data suggest that exacerbation of asthma especially in children has dramatically decreased during the COVID-19 pandemic, which may be not only related to decrease in exposure to triggers, such as other respiratory viruses and air pollutants but also may be related to improved adherence to controller therapy [44,47,48]. Management of exacerbations of asthma in the era of COVID-19 includes risk assessment and defining severity of the disease. According to BTS and the Global Initiative for Asthma (GINA) [49] patients with exacerbation can be treated with a burst of oral prednisone or quadruple their inhaled corticosteroid dose as part of a personalized asthma action plan. Follow-up and safety-netting are crucial in providing guidance to next steps in case of deterioration, and it is recommended that all patients are followed up within 24 h via remote assessment. Severe exacerbations (RR >25, pulse >110, inability to complete full sentences, PEF <50% of best or predicted) entail a face to face assessment or immediate hospital referral in case of life-threatening symptoms [50▪▪,51,52,53].

Management of stable patients with asthma

Corticosteroids use

The appropriate management of stable asthma in the era of COVID-19 was debated, particularly regarding the safety of corticosteroid use. Whilst mixed data exist on the association between ICS use in asthma and the risk of developing respiratory infections and increased risk of viral replication, presently, there is no evidence with their association of increased risk of COVID-19 infection. In addition, and as aforementioned, a lower expression of ACE2/TMPRSS2 receptors was reported in patients with asthma who are using ICS [17]. In a systematic review of patients with stable asthma, the discontinuation of ICS was associated with more than double the risk of getting asthma exacerbations (RR 2.35, 95% CI 1.88–2.92) [54▪]. Therefore, current consensus is to continue using ICS in an effort to maintain control of the disease and prevent any asthma exacerbations [55]. Systemic corticosteroids can also be used in moderate-to-severe asthma exacerbations and are presently not perceived as a contraindication in concomitant SARS-CoV-2 infection, especially that have been shown to reduce mortality in patients hospitalized with severe COVID-19

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needing intubation and/or high level of oxygen support [56].

With regard to nasal corticosteroids, the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) concluded that proper treatment of allergic rhinitis and allergic asthma is important and topical corticosteroids can be used in such cases [57▪▪].

Allergen immunotherapy

Allergen immunotherapy (AIT) may provide a possible theoretical advantage to patients during COVID-19 pandemic and can be continued as long as patients are not diagnosed with COVID-19. Initiation of AIT in eligible patients is preferred to be in sublingual form if possible, in order to minimize in-person encounters for subcutaneous injections [58,59]

Aerosolized medications: strategies for well tolerated and effective delivery

Although the infection with SARS-CoV2 is transmitted by droplets, aerosols transmission is also plausible, given data on the viability of the virus for hours in aerosols. Aerosolized medications are at the mainstay of the management and treatment of asthma and other respiratory diseases. Aerosols are transmitted during patient expiration after use of aerosol devices in a process called fugitive emission. Factors affecting the quantity of fugitive emissions include the device interface, patient's flow rate, air turbulence, etc. Therefore, healthcare workers can be within a radius of risk if aerosolized medications are delivered. Practical strategies have been developed to avoid unnecessary risk for healthcare providers and to ensure adequate delivery and effectiveness of medications to patients with asthma. As mentioned above, if aerosol therapy is used, it should be administered in negative pressure rooms with adequate ventilation with the use of personal protective equipment [60].

In the hospitalized setting, the use of metered dose inhalers (MDIs) and dry powder inhalers (DPIs) is preferred over nebulizers if patients are able to perform the breathing maneuvers. If a nebulizer is used, high flow nasal cannula is preferred over a face mask and a mouthpiece is preferred to be used with a jet or mesh nebulizer. Viral filters or one-way valves should be attached to nebulizers to minimize the release of aerosols. For ventilator-dependent patients, the use of MDIs and/or jet nebulizers should not be used as breakage of the circuit occurs in order to place the devices. Mesh nebulizers on the other hand can stay in-line for 28 days and are preferred in ventilated patients. Filters should be attached to the expiratory limb of the ventilator to reduce transmission of aerosols [61].

Biological therapies

Another facet in the management of patients with severe asthma during this pandemic is the safety status of the biological therapies especially regarding any risk of increasing the susceptibility to contracting COVID-19, and in case infected the risk of a more severe outcome.

Of the current approved classes of biological therapies in severe asthma, IL5 antagonists (mepolizumab, reslizumab) and IL5 receptor antagonist (benralizumab) work mainly on the depletion of eosinophils and their subsequent type 2 inflammation markers [62]. At a mechanistic level, and as previously mentioned, type 2 inflammatory biomarkers had mixed effects on the expression of ACE2 and TMPRSS2 receptors with no clear balance effect [20,63]. As already discussed, eosinopenia has been associated with worse prognosis in patients with COVID-19. However, as this is more thought to be related to the effect of the infection itself, treatment modalities while they deplete eosinophils (which *per se* may have a protective role against viruses [64]), do not seem to increase the susceptibility to acquiring infection or adversely affect outcomes. Therefore, in the present absence of any data indicating a potential harm of IL5/anti-IL5R antagonists, and with the fear that stopping these biologics can affect disease control, continuation of therapy as part of benefit to risk assessment is recommended. However, individualized precautions and close monitoring of patients are recommended [50▪▪]. The same rationale applies to the IL4 R-α antagonist, dupilumab [50▪▪,65].

Omalizumab, a monoclonal antibody that selectively binds human immunoglobulin E (IgE), is another biologic used in severe asthma. Interestingly, recent studies showed an effect of anti-IgE on the reduction of the rhinovirus illnesses in children with allergic asthma and shortening the illness duration if it happens, along with minimizing viral shedding [66]. The interplay between anti-IgE and interferon levels was postulated to be contributing to the viral clearance. In addition, anti-IgE was shown to reduce lower respiratory tract symptoms in patients inoculated with rhinovirus-16 (RV16) [67]. Whereas no data exist on the association between anti-IgE therapy and COVID-19, consensus is to continue to use omalizumab during the pandemic [65]. Whether the protective role of anti-IgE on rhinovirus viral clearance can be extrapolated and generalized to SARS-CoV-2 needs further investigations and studies.

General strategies on the pharmacologic management of asthma during the COVID-19 pandemic are outlined in Fig. 1.

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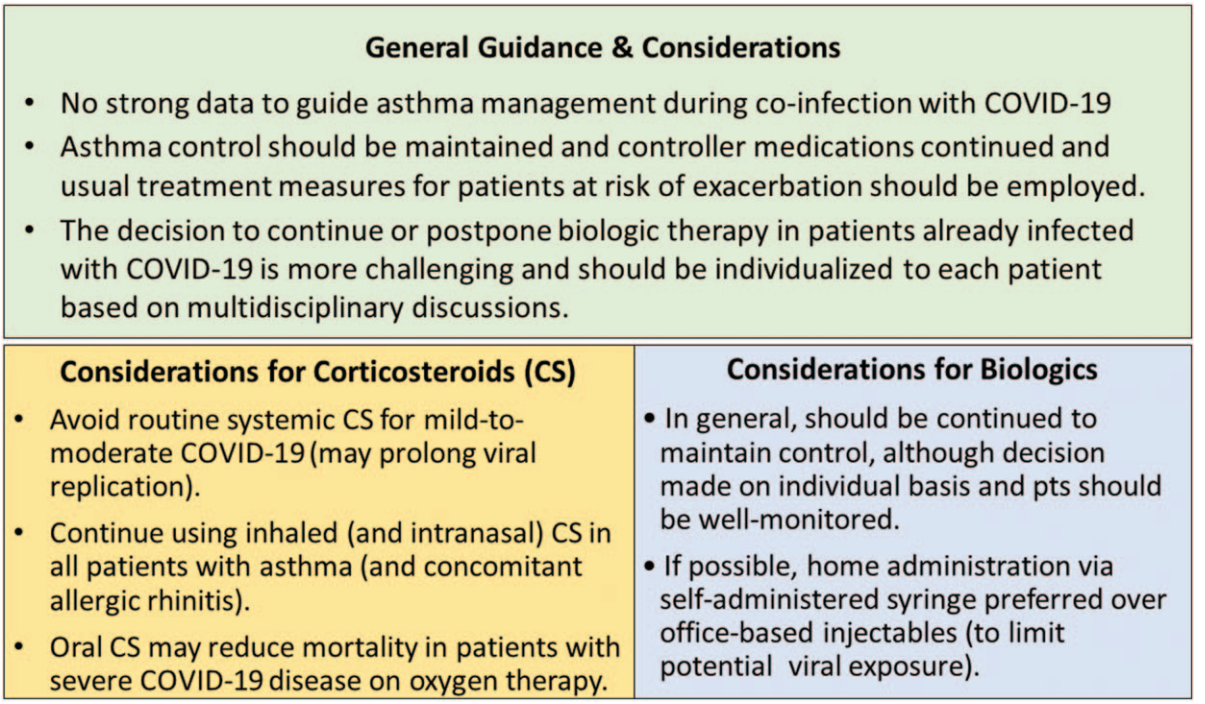

FIGURE 1. Current considerations for the management of asthma during coronavirus disease 2019 pandemic. Data from [49,50▪▪,57▪▪].

CONCLUSION

Current evidence indicates that asthma has not been consistently associated with increased risk for COVID-19 or with poor outcomes, such as hospitalization and mortality. Emerging data also suggest that while underlying type-2 airway inflammation associated with decreased ACE2 expression in some patients may reduce their risk to SARS-CoV-2 infection, and that patients with nonallergic (non-type 2) asthma may indeed be at increased risk. However, such observations emerged from studies evaluating the expression of the ACE2 receptors on airway cells and in biological specimens obtained from large existing asthma cohorts, and thus need to be further validated in future prospective studies.

In summary, management of asthma in the era of COVID-19 should not change. Although the use of corticosteroids in asthma was initially controversial, it is now evident that their use may, in fact, confer a protective role in asthma by downregulating the ACE2/TMRSS2 receptors and thus their use should be maintained. The benefits and risks of administering biologics during the COVID-19 pandemic have not been systematically examined. Consensus recommendations suggest that they should continue to be administered unless the patient is infected with SARS-CoV-2 when their use has to be individualized based on multidisciplinary discussions. In addition, changes in behavior of patients with asthma during the COVID-19 pandemic lockdown, such as improved adherence to controller medications and reduced exposures to other viruses and air pollutants because of isolation have indeed been associated with improved asthma control and reduced exacerbations and health care utilization. Future studies should identify specific phenotypes/endotypes of asthma at increased risk of COVID-19 and determine any potential protective benefit and risk of existing biologics in such populations. Furthermore, the effect of SARS-CoV-2 vaccine, once it becomes available, on asthma outcomes also needs to be examined.

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Conflicts of interest

Z.D. until Q1-2020, was Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies. In addition, Z.D. received honoraria, consultancy and speaker fees from Acucort, Astrazeneca, ALK,

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Aquilon, Boehringer Ingelheim, CSL, GSK, HAL Allergy, MSD, Sanofi-Genzyme. N.A.H. received honoraria for serving as a consultant or advisory boards for GlaxoSmithKline, Sanofi, Regeneron, Genentech, Novartis, Boehringer Ingelheim, Astra Zeneca and Mulan pharmaceuticals. His institution receives research grant support from GlaxoSmithKline, Sanofi, Genentech, Gossamer Bio, Boehringer Ingelheim, Novartis and Astra Zeneca.

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