Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Perspective

Asthma, biologics, corticosteroids, and coronavirus disease 2019

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As coronavirus disease 2019 (COVID-19) continues to spread across the world, there are concerns that patients with asthma will be at higher risk for the disease or poorer outcomes. There is also concern about whether asthma treatments themselves could worsen the risk of disease or severity.

Current evidence indicates that asthma is not in the top 10 comorbidities associated with COVID-19 fatalities, with obesity, diabetes, and chronic heart disease more commonly reported.[1] This finding is consistent with trends during the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic, caused by a virus with close sequence homology to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), during which diabetes and heart disease and not asthma were the leading comorbidities.[2] However, comorbidities found with COVID-19 fatalities may reflect confounding by age, and the Centers for Disease Control and Prevention has reported that among younger patients hospitalized for COVID-19 the most common comorbidities were obesity, asthma, and diabetes.[3] Although the role of asthma in increasing the severity of COVID-19 infections remains unclear, anxiety continues to be high among patients and their caregivers.

These concerns are not baseless. Asthma may increase the risk of developing viral respiratory illnesses, and even human rhinovirus, the most common cause of the common cold, is a potent trigger of asthma exacerbations.[4] Synergism between allergen sensitization and viral infections in patients with allergic asthma, weaker antiviral defenses, and lower interferon production, all seem to contribute to the higher risk of viral infections in patients with asthma.[4] Allergic sensitization and eosinophilic inflammation can breach the integrity of the airway epithelium, contributing to a milieu that may foster viral infections that involve the lower airways and limit the ability of the respiratory tract to appropriately clear viruses. Although the usual coronavirus infections are more likely confined to the upper airway, the predilection for COVID-19 to infect the lower airway, even in healthy individuals, creates even greater concern in patients with asthma.

Additional questions of concern relate to the effects that asthma medications may have on COVID-19 infections. Inhaled corticosteroids are the mainstay of treatment of persistent asthma, and oral corticosteroids are frequently used during acute exacerbations.[5] Multiple in vitro studies have found that corticosteroids inhibit viral-induced cytokines but do not inhibit interferons, which are an important antiviral defense mechanism.[5] Despite these inhibitory effects and the overall efficacy of corticosteroids, patients with asthma well-controlled with inhaled corticosteroids can still have virally induced exacerbations.

As an added concern, corticosteroids produce a dose-response increase in the risk of pneumonia in patients with asthma, and asthma itself is an independent risk factor for severe pneumococcal disease.[6] Pneumonia is not an uncommon feature of COVID-19, but whether asthma and corticosteroid use would increase the risk of secondary bacterial infection with COVID-19 remains to be determined. Given the current state of information, it is impossible to make conclusive statements about the effect corticosteroids might have on the disease course of any patient with asthma. For instance, the timing of steroid administration during the course of human rhinovirus–induced illness considerably affects suppression of cytokine production and inflammation.[5] Indeed, current expert guidelines discourage the use of corticosteroids in the treatment of COVID-19 in patients in general.[7] For patients with asthma treated

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Table 1
Current Gaps and Future Direction in COVID-19 Treatment

Current gap or issue	Future direction
To date, COVID-19–related studies have combined patients with asthma and chronic obstructive lung disease, making the effect of asthma on COVID-19 outcomes unclear	Pursue studies that isolate the effect of asthma from chronic obstructive lung disease in COVID-19 severity and outcomes
Emerging evidence suggests that asthma is underrepresented as a comorbidity in COVID-19 fatalities	Evaluate age-stratified incidence rates and fatality rates of COVID-19 among patients with and without asthma
Unclear how maintenance medications, including inhaled or oral corticosteroids and biologics affect risk, severity, and outcomes of COVID-19	Conduct epidemiologic studies describing disease course in patients on these medications Perform mechanistic studies that might help answer these questions
Post–COVID-19 respiratory sequelae are unclear	Prospectively follow patients to determine pulmonary outcomes and sequelae after COVID-19 infection
Racial and ethnic minorities are more likely to die of COVID-19	Explore racial and ethnic disparities in outcomes from COVID-19 infection in patients with asthma

Abbreviation: COVID-19, coronavirus disease 2019.

with inhaled corticosteroids, both the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology recommend that patients continue to use their maintenance medications even during the pandemic.[8] Continuation of therapy even with potential exposure to COVID-19 is extremely important because poorly controlled asthma is always the greatest risk factor for exacerbations with any viral infection.

With regard to biologics approved for asthma treatment, effects on the risk of COVID-19 may differ. Omalizumab (an anti–immunoglobulin E [IgE] antibody), mepolizumab and reslizumab (which block interleukin [IL] 5), benralizumab (which blocks the IL-5 receptor), and dupilumab (which blocks IL-4 receptor α, a receptor shared by IL-4 and IL-13) 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.[4,5] Thus, these effects on overall exacerbations suggest that these biologics may affect virally exacerbated disease. This effect has been best established for omalizumab, which prevents IgE from binding to its receptor on plasmacytoid dendritic cells. Cross-linking of IgE leads to lower type 1 interferon production, and in clinical studies, omalizumab has been found to decrease the risk of, duration, and viral shedding of human rhinovirus in children with allergy.[9]

Mepolizumab, reslizumab, and benralizumab also potentially play a role in enhancing immune responses to viral infections given that a higher ratio of interferon gamma to IL-5 messenger RNA is associated with lower viral shedding and faster disease clearance.[10] In addition, recognizing that IL-5 plays an essential role in airway eosinophilic inflammation, its inhibition may make the airway less susceptible to additional lung injury from diseases such as COVID-19.[10] Dupilumab decreases airway inflammation, allergic airway response, and asthma exacerbations. Interleukin 4 is vital for antibody switching to IgE, and IL-13 is a T_H2 cytokine involved in airway hyperresponsiveness and in airway remodeling, all of which are involved in susceptibility to and clearance of lower airway viral infections.[4] Thus, it is likely that these biologics will lessen the risk of severe asthma exacerbations with COVID-19, at least by reducing baseline airway inflammation and possibly through specific antiviral properties.

SARS-CoV-2 is an enveloped virus of the extremely diverse family of coronaviruses. Mapping of the mechanism of COVID-19 clearance by the immune system of a patient who recovered from COVID-19 found that immunoglobulin M and immunoglobulin G antibodies to SARS-CoV-2, follicular T-helper cells, and antibody-secreting cells were all detected in the patient's blood before recovery.[11] With our knowledge of how the currently approved biologics work, we do not believe that these medications would interfere adversely with any of these pathways or worsen an individual's immune response to COVID-19. It is actually plausible that these biologics, by limiting T_H2 skewing, may make the immune system better poised to clear SARS-CoV-2. Although the immune mechanisms for COVID-19 are yet to be fully defined, it is less likely that these biologics will interfere with the pattern-recognition receptor system by which the innate immune system recognizes pathogen-associated molecular patterns.

We admit that current data on the risk of acquiring COVID-19 or disease severity in patients with asthma are limited. Key areas for future research are highlighted in Table 1. From previous knowledge and mechanistic studies, the effect of steroids on the risk of acquiring COVID-19 and the outcomes of COVID-19 infections would likely depend on multiple individual-level factors, most importantly baseline asthma control and possibly the dose of steroid used. We do not believe any of the currently approved biologics for asthma treatment would increase the risk of disease or worse outcomes. On the contrary, we postulate that the reversal of the T_H2 skew and the improvement in airway allergic and eosinophilic inflammation and bronchial responsiveness induced by these biologics could be advantageous in patients with asthma who are already taking these medications before contracting COVID-19. Nonetheless, patients with asthma need to continue to exercise extreme caution while we make efforts to learn more and quell this pandemic.

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