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Editorial

Asthma and COVID: What Are the Important Questions?

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The COVID-19 pandemic has created a global crisis that has led to substantial morbidity and mortality and has devastated health systems and economies. In response, the global scientific community has mobilized to seek insights to better understand, limit, and treat this disease. In severe SARS-CoV-2 infection, a complex immunopathology exists that comprises active viral replication and an armed, overactive immune, and inflammatory response.[1] Cytokines (such as IL-6 and IL-1) can evoke a cytokine storm syndrome (CSS) that features elevated markers of inflammation (such as high sensitivity C-reactive protein, lactic dehydrogenase, and ferritin) and an acquired immunodeficiency (eg, lymphopenia with reductions in T cells). Disruption of the coagulation cascade (fibrinogen, factor VIII, and platelets) in CSS can lead to a coagulopathy with elevated D-dimers and fibrin split products, reflecting a generalized severe endovascular process.[2] Tissue injury may then ensue from macro- and microthrombi in the veins and arteries of major organs including the lungs, heart, kidneys, and brain. Evidence of CSS is present in a high proportion of severely ill patients.[3] However, critical questions remain about the biologic and clinical features that predispose to CSS and critical illness, including underlying comorbidities such as asthma and the medications used to treat them.

Older age and comorbidities, especially heart disease, hypertension, chronic obstructive pulmonary disease (COPD), diabetes, and obesity, are reported risk factors for the development and progression of COVID-19.[4] However, controversy exists as to whether patients with asthma manifest high or elevated rates of COVID-19 incidence. Surprisingly, limited data exist that patients with severe asthma with markedly diminished lung function and receiving monoclonal antibodies are at greater risk than those with less severe disease. Are there pathophysiological or pharmacological mechanisms that could explain why asthma, compared with non-asthma, patients may be less or no worse infected by SARS-CoV-2? Clearly, more questions than answers exist.

COVID-19 DISEASE AWARENESS AND CONSEQUENCES

World news has focused attention on the consequences of COVID-19 in vulnerable populations. As a consequence, patients with asthma may become hypervigilant on personal hygiene and social distancing. Social distancing could improve asthma control because individuals quarantined at home have diminished exposure to seasonal triggers that include other respiratory viruses or allergens. Evidence also suggests that the pandemic enhances asthma medication adherence.[5] Thus, the pandemic may have paradoxically improved some clinical outcomes of asthma management due to improved trigger remediation and medication adherence.

USE OF INHALED CORTICOSTEROIDS

Inhaled corticosteroids, a mainstay in the management of asthma, may directly modulate SARS-CoV-2 infectivity. *In vitro* models and drug library screening approaches suggest that ciclesonide decreases SARS-CoV-2 replication. Inhaled corticosteroids have also been associated with decreased expression of angiotensin-converting enzyme 2 (ACE2), the coreceptor for SARS-CoV-2 raising the question of whether these drugs could decrease viral susceptibility.[3] Corticosteroids may decrease innate immune responses and worsen viral-induced inflammatory response in a rodent model. Moreover, corticosteroids delay viral clearance of SARS and Middle East respiratory syndrome from the human respiratory tract and may worsen COVID-19 outcomes. Future studies should address whether inhaled corticosteroids in patient with asthma and/or allergic rhinitis increase or decrease risks of SARS-CoV-2 infection, and whether these effects different across inhaled steroid types. Analyses of real-world data from health and pharmacy benefit claims could address these critical questions.

AGE

Susceptibility and severity to COVID-19 infection increases with age.[4] Because asthma sufferers tend to be younger than those with other comorbidities, is age a factor in explaining why patients with asthma may not be at greater risk? To address this question, age-adjusted models need to be formulated. Children and young adults with asthma manifest T2 high airway inflammation that is driven predominantly by allergy, IL-4 and IL13. In comparison, older adults who can have T2 high airway inflammation also manifest an eosinophilic phenotype and other

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comorbidities of chronic rhinosinusitis with or without nasal polyps. In addition, expression of ACE2, the coreceptor for SARS-CoV-2, varies with age, and ACE2 expression is increased by interferons, thought to be beneficial in clearing other respiratory viruses especially in children.[3] Whether these pathogenic mechanisms affect SARS-CoV-2 infectivity in individuals with asthma remains unclear.

ASTHMA AND COMORBIDITIES

Asthma tends to be associated with far fewer comorbidities than COPD or cardiovascular disease (CVD). This observation could be a function of patients' age or relate to the strong associations between COPD, CVD, and adverse lifestyles/habits. If SARS-CoV-2 is a disease manifested by systemic consequences of endothelial cell dysfunction, then diabetes, heart disease, obesity, and other diseases associated with endothelial dysfunction may engender more susceptibility than asthma.[1] By extension, older individuals with asthma who also have hypertension, diabetes, or heart disease should manifest similar incidences of COVID-19.

In sum, whether asthma represents a comorbidity associated with susceptibility to and progression of COVID-19 remains unclear. The tropism for SARS-CoV-2 to the upper airway epithelium and the use of inhaled corticosteroids provide a real life laboratory to test whether these attributes modulate infectivity and disease progression. More research is needed to address the characteristics of those with asthma who develop COVID-19 and how asthma therapy, including inhaled corticosteroids or biologics, modulates such risks.

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