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Asthma and COVID-19: Preconceptions about Predisposition

It is now just past 15 months since coronavirus disease (COVID-19) was identified in China and rapidly spread throughout the world. There has been an extraordinary research effort to understand the pathophysiology of COVID-19, providing an evidence base on which to develop public health, therapeutic, and vaccine interventions. The burden of COVID-19 falls disproportionately on different populations, and research has sought to rapidly identify those at higher risk, such as those with specific comorbidities.

The situation with asthma was intriguing from the outset of the pandemic, with initial case series either not reporting that COVID-19 infections provoked severe exacerbations of asthma (1, 2) or specifically reporting that patients hospitalized with COVID-19 did not present with severe asthma exacerbations (3). These observations were unexpected, as viral respiratory tract infections are the most common cause of severe exacerbations of asthma. Specifically, *Coronaviridae* are associated with up to 13% of asthma exacerbations in children (4) and up to 16% in adults (5).

Whether people with asthma represented a high-risk population came into sharp focus when chronic obstructive pulmonary disease was strongly associated with severe disease, ICU admission, and death (6, 7). However, a similar risk was not identified with asthma when adjusted for other variables, although asthma with recent oral corticosteroid use increased the risk of mortality from COVID-19 in one study (8).

These reports were followed by a systematic review and meta-analysis of COVID-19 studies that reported outcomes in patients with asthma and had been published by August 18, 2020 (9). The main findings of this review were that asthma was not associated with higher COVID-19 severity and that patients with asthma had a lower risk of death. Knowledge in this field has now been extended with the publication by Terry and colleagues (pp. 893–905) of a systematic review and meta-analysis of studies in this issue of the *Journal* that examined the prevalence and/or risk of severe disease in adult patients with asthma and COVID-19 (10). Advantages of this current review include the availability of considerably more studies for inclusion in the meta-analysis, the comparison with asthma prevalence rates in the broad populations studied, and the use of multivariate modeling in the subset of studies of asthma and COVID-19 mortality.

First, the authors report that their findings suggest the possibility of a moderate decreased risk of a COVID-19 diagnosis in

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adults with asthma, although they acknowledge the major limitations with the analyses on which this interpretation is based. Specifically, accurate comparisons cannot be made between the prevalence of asthma reported in local studies of acutely unwell COVID-19 populations and the crude asthma prevalence in general population surveys based on provincial, country, or continental estimates, in which there is no standardization of the diagnostic methods used and no age-, sex-, or ethnicity-matched populations.

Second, the authors report that there was no significant increased risk of "severe disease" or hospital admission. The studies analyzed provided little information on the asthma phenotype, which meant that it was not possible to further investigate the observation that patients with nonallergic asthma experience worse outcomes than those with allergic asthma (11).

Third, the authors report a significant 18% (95% confidence interval, 0.15–0.22) reduction in risk of mortality in patients with asthma and COVID-19. This finding is more robust because of the adjustment for major confounding factors, and it provides reassurance to people with asthma and those responsible for their care.

These findings raise the question as to how asthma may lead to a possible reduction in developing symptomatic COVID-19 and a probable reduction in its mortality risk. Different hypotheses have been proposed, including behavioral reasons, lower expression of ACE2 (angiotensin-converting enzyme 2; the cellular receptor for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) in asthma, altered T1 immunity as a result of complex interactions with the enhanced T2 immune response in asthma, mucus hypersecretion reducing exposure to SARS-CoV-2 in the distal lung, and the effects of treatments such as inhaled corticosteroids (ICS) (12, 13).

The issue as to whether ICS may reduce the risk of SARS-CoV-2 infection progressing to severe COVID-19 is particularly intriguing. On the one hand, this seems counterintuitive when the increased risk of pneumonia in asthma and chronic obstructive pulmonary disease with ICS therapy is considered. However, there is some evidence to suggest ICS reduce the expression of ACE2 and TMPRSS2 (transmembrane protease serine 2), the protease involved in cell entry (14). If these or other mechanisms resulted in clinical benefit, it would have major therapeutic implications well beyond asthma, as there is a paucity of effective and safe therapeutic interventions that modify the natural history of the disease and reduce the risk of hospitalization for those with COVID-19 managed in the community.

Relevant to these considerations is the importance of nonpharmacological interventions and their potential impact on respiratory health beyond COVID-19. The New Zealand experience has shown that strict public health measures (such as widespread mask use, school and workplace closures, physical distancing, travel restrictions, and limits on gathering sizes) can dramatically reduce the risk of community transmission of not only COVID-19 but also respiratory infections such as influenza (15, 16). The potential impact can be marked, with almost no influenza cases during the winter of 2020 (16) and an overall 11% reduction in all-cause mortality in New Zealand with the strict public health measures (17). These observations demonstrate the effectiveness of individual and community actions in reducing the impact of respiratory infections on those with asthma. Recent Global Initiative for Asthma (18) recommendations outline steps we can take to ensure good outcomes for patients with asthma in the context of COVID-19. Indeed, Terry and colleagues' review (10) strengthens the Global Initiative for Asthma advice, which can be recommended as an evidence-based template on which to base our individual approach to the management of asthma in this pandemic era. This review has also shown how a novel virus such as SARS-CoV-2 can give rise to surprising observations, such as the probable reduced risk of morbidity and mortality in patients with asthma, that highlight gaps in our knowledge of the interplay between viral infections and asthma. ■

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Richard Beasley, D.Sc.
Medical Research Institute of New Zealand
Wellington, New Zealand

Thomas Hills, D.Phil.
Department of Clinical Immunology
Auckland District Health Board
Auckland, New Zealand

Nethmi Kearns, MBChB
Medical Research Institute of New Zealand
Wellington, New Zealand

ORCID IDs: 0000-0003-0337-406X (R.B.); 0000-0003-0322-5822 (T.H.); 0000-0002-3188-991X (N.K.).

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