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## Theme Editorial

# Perspectives in Respiratory Infections and the Lung

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Respiratory infections are common, usually involve the upper respiratory tract, and, in most cases, are self-limited and well tolerated. However, in at-risk patients with asthma, respiratory tract infections can provoke symptoms and airflow obstruction that may be profound and debilitating. Furthermore, when respiratory infections directly infect the lung, morbidity can be significant and even lead to death. The scope, influence, and contributions of respiratory infections to compromises in life-sustaining function of the lungs have been dramatically, and catastrophically, demonstrated with the ongoing coronavirus disease 2019 (COVID-19) pandemic from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For the readers of the *Journal of Allergy and Clinical Immunology*: *In Practice* (*JACI: In Practice*), the clinical implications of respiratory infections and the lung are well known and appreciated, and encompass an important component of clinical and research endeavors. The resulting advances have led to greater mechanistic insights, contributed to a greater recognition and appreciation of the effects of respiratory infections on the lung, and lastly, but most important, improved patient outcomes. The 4 articles of this thematic issue serve to underscore the importance of Respiratory Infections and the Lung to readers of *JACI: In Practice* and serve to provide information valuable in patient care

Respiratory infections are linked to many aspects of asthma's life cycle: early wheezing episodes, potential risks in the development of asthma, and a major cause of exacerbations.[1] Respiratory infections closely linked to asthma pathogenesis and pathophysiology include respiratory syncytial virus (RSV) and rhinoviruses (RVs). Both RSV and RVs cause early-life wheezing episodes. Whether these early-life infection-provoked wheezing events contribute to, or cause an eventual development of, asthma is not established, but ascertainment of these relationships stresses the importance of respiratory tract infections to an eventual expression of asthma and has identified other key risk factors—genetic determinants, environmental factors, and immunoinflammatory generation—in determining links to asthma pathogenesis. In contrast, the striking relationship of viral respiratory infections to asthma exacerbations is firmly established and provides a portrait of how respiratory viruses can affect the generation of airway inflammation. Guided therapeutic targets of this virus-induced inflammation may provide more precise treatment.[2]

The health-altering consequences of respiratory infections on the lung are largely determined by functions of the host's immune-protective response. Patients with primary immune deficiencies diseases (PIDDs) are at particular risk for severe consequences from respiratory infections, which often serve as a precipitating event for the presence of defective immune function. Institution of newborn screening has helped identify at-risk infants for PIDDs to prevent unexpected severe respiratory illnesses with early-life infections. Identifying and defining immune deficiencies associated with infections of the lungs has also contributed to greater insights into specificities of protective immune function and direction to improve treatment strategies.

The ongoing 2-year COVID-19 pandemic has driven home the importance, susceptibility, and devastating consequences of respiratory infections of the lung with SARS-CoV-2. Through this work has emerged implementation of molecular diagnostics and novel vaccination strategies to more precisely, and effectively, prevent disease. In the COVID-19 pandemic, patients with asthma have been of particular interest because of the history of susceptibility to other viral infections in asthma. Because Respiratory Infections and the Lung represents a major portion of all aspects of allergy and immunology, we feel the collective discussion of this topic will be of broad interest and importance to *JACI: In Practice* readers.

To introduce the Clinical Commentary Reviews of Respiratory Infections and the Lung, we have highlighted key messages from each of the 4 articles. Achten et al[3] discuss "Long-term Consequences of Early-Life Respiratory Viral Infections: A Pragmatic Approach to Fundamental Questions." The authors focus their discussion on a fundamental and pivotal question as to whether wheezing with respiratory infections in infancy and early childhood causes asthma, and if causative data exist, would a prevention of early-life respiratory infections diminish the risk for asthma? Clinical and research observations find links between viral infections in infancy as a possible heralding event to asthma.[1] If this causative association were established, potential guidelines to prevent asthma, or at least alter components of disease expression, could be developed. As the authors state, although this question has not been answered, efforts to probe the relationships between early-life respiratory infections and asthma development have provided valuable insight into the association of RSV infections to lung development and altered airway function. RSV infects the airway epithelium to alter pulmonary functions. Also associated with an RSV infection is a

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skewing of the immune response toward a type (T) 2 inflammation along with heightened IL-17A production, a pattern of airway inflammation linked to asthma.[4] However, as the authors point out, it may not be only the infecting virus but other factors that determine or contribute to a resulting pattern of airway dysfunction. Of particular interest has been the pattern of the existing or altered microbiota that determines an eventual long-term response, as well as host genetic factors. Although the answers to whether RSV leads to asthma are not established, the authors note that "clinical care will need to continue to focus on optimal treatment of childhood wheezing disorders until there are proven preventative interventions."

Jackson and Gern[5] extend the discussion on the role of respiratory infections and the lung in "Rhinovirus Infections and Their Roles in Asthma: Etiology and Exacerbations." RVs are the most common cause of respiratory infections. For most people, the common cold produces a mild illness with symptoms limited to the nose. In asthma, the effects of a RV infection can be profound and provoke an exacerbation. In addition, RVs have emerged as potential contributors to the development of asthma when allergic sensitization exits. In their comprehensive review, Jackson and Gern[5] identify key determinants that cause asthma exacerbations, which begin with the RV infecting airway epithelial cells and stimulating the generation of alarmins, especially IL-33, to propagate T2 inflammation of the airway to provoke airflow obstruction. The pathways through which RVs promote T2 inflammation and how this virus-driven inflammatory response occurs in susceptible patients with asthma to provoke asthma has been clarified over the past 2 decades.[2] These observations provide direction for more precise treatment and have served as a mechanistic footing for the effective use of anti-T2 biologics in high-risk, exacerbation-prone patients with asthma. Insight into why some patients with asthma are more susceptible to the untoward effects of a viral respiratory infection has followed a recognition that defective antiviral responses exist in asthma. Interferons are important host defense combatants of viral infections. Evidence has emerged for the presence of defective or diminished generation of type I and III interferons in asthma.[6] The presence of defective immune responses as contributors to increased susceptibility to respiratory infections should not be a surprise given experiences from PIDD.

Lehman et al[7] provide a key commentary on "Respiratory Infections in Patients with Primary Immunodeficiencies (PIDD)."[7] The authors remind us that respiratory tract infections are often a presenting manifestation of an underlying, unrecognized PIDD. The scope of micro-organisms that cause respiratory illnesses in PIDD is broad, for example, bacteria, viruses and fungi, with the dominant infecting organism related to the characteristic of the primary immune deficiency, humoral versus cellular. A first step to identify a PIDD in patients with difficult-to-treat respiratory infections is a focused evaluation that should always include a heightened awareness and suspicion of immune deficiencies. Newborn screening provides for an early identification of PIDD and has prevented delays in diagnosis to facilitate earlier treatment and a prevention of morbidity, mortality, and potential long-term effects on the lungs. Two tables are included in their article to provide helpful information on what to consider when evaluating findings of an infection by chest computed tomography (Table I) as well as guidelines to targeted therapies in PIDD (Table II). Table II is particularly helpful because it lists the infectious agent (virus, bacteria, or fungi), the therapies recommended for the immunocompetent host, and additional considerations for immunodeficient patients. The guidance in Table II provides direction for initial treatments in PPID. The authors also discuss recent advances in the development of mRNA vaccinations, which are proving efficacious, and may be beneficial strategies for selected patients with PIDD.

The COVID-19 pandemic has grabbed the attention of the whole world with the devastating consequences of a highly virulent and transmittable respiratory virus whose infection of the lung is a primary determinant of patient outcomes. Molecular diagnostics are now available to rapidly identify the presence of microbial organisms, define their genetic structure, and recognize the emergence of mutant variants. Although certain patient populations are at high risk, for example, the elderly, minorities, those with coexistence of diabetes, and immune suppression, virtually anyone and everyone is at risk for serious consequences of a COVID-19 infection. Of particular interest to the readership of *JACI: In Practice* has been concerns for increased risks in asthma. Palmon et al[8] address this topic in their discussion on "COVID-19 Infections and Asthma."[8] The concern with asthma is based on its known vulnerability to viral infection provoked exacerbations. Currently, there does not appear to be an increased risk for worse outcomes in patients with asthma infected with COVID-19, other than in the presence of uncontrolled or severe asthma. What has also emerged has been observations that COVID-19 infections may not be a particular risk in all patients with asthma or those with underlying allergic diseases.[9] The primary respiratory epithelial receptor for SARS-CoV-2 is the angiotension-converting enzyme-2 (ACE2) receptor. An inverse relationship between ACE2 receptor expression and the presence of aeroallergen sensitization has been found.[10] These observations suggest that mediators/cytokines associated with T2 inflammation, IL-13 in particular, regulate ACE2 receptor expression. The effects of these mediators on ACE2 receptor expression may explain why patients with allergic disease and asthma are not overly susceptible to COVID-19 because the ACE2 receptor may be downregulated. A translation of T2 inflammation and COVID-19 interactions to improved clinical outcomes is under investigation; these observations further indicate how major infections, as was observed with HIV, provide opportunities to elucidate immune responses to infections. This knowledge has been translated to more effectively understand mechanisms of infection and to provide guidance to prevent the development of life-threatening pneumonias.

We are grateful to the authors and their expertise, which has effectively addressed and clarified the important topic of Respiratory Infections and the Lung. We have enjoyed reading of the advances in the relationship of infections and the lung and how the impact of these discoveries has led to an expanded knowledge and improved patient care. We hope that the readers of *JACI: In Practice* will find this theme as beneficial as we have.

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